Neurocognition and Social Functioning in Bipolar Disorder at First Treatment Contact

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LIST OF PAPERS

I. Hellvin, T., Sundet, K., Vaskinn, A., Simonsen, C., Ueland, T., Andreassen, O.A. and Melle, I. (2010). Validation of the Norwegian version of the Social Functioning Scale (SFS) for schizophrenia and bipolar disorder. *Scandinavian Journal of Psychology,* 51, 525-533.

II. Hellvin, T., Sundet, K., Simonsen, C., Aminoff, S.R., Lagerberg, T.V., Andreassen, O.A. and Melle, I. (accepted for publishing in Bipolar Disorders). Neurocognitive functioning in patients recently diagnosed with bipolar disorder.

III. Hellvin, T., Sundet, K., Aminoff, S.R., Andreassen, O.A. and Melle, I. (submitted). Social functioning in first contact mania: clinical and neurocognitive correlates.

SUMMARY

Neurocognitive impairment and social dysfunction has been reported in patients with bipolar disorder, and several studies have reported a relationship between neurocognition and social functioning in this group. Although some studies had suggested neurocognitive and social dysfunction in the early phases of bipolar disorder, there was little research on bipolar disorder patients diagnosed with a first manic episode at the planning of this thesis. The studies of social functioning in bipolar disorder had also been disadvantaged by the multitude of different assessment instruments in use. The first aim of study was therefore to establish reliability and validity of the Norwegian version of a well-known assessment instrument for social functioning – the Social Functioning Scale. The scale, originally developed for schizophrenia patients, was found to have good psychometric properties and was applicable for patients with bipolar disorder as well as for patients with schizophrenia. Although studies of neurocognition in the early phases of bipolar disorder were few, the existing literature had reported neurocognitive deficits in first-episode mania. Studies comparing neurocognitive functioning in first-episode patients to multiple-episode samples were few and inconclusive, and few studies had investigated to what degree first-episode patients showed *clinically significant* cognitive impairment. The second aim of the study was to describe neurocognitive functioning and the magnitude of dysfunction in a group of patients with first contact mania to an age, gender and education matched sample of healthy control participants. Patients were separated into two groups according to their number of previous manic episodes – one group consisting of patients with only one previous manic episode (First Manic episode; FM), and a second group with patients who had experienced multiple although untreated previous manic episodes (Previous manic episode; PM). Consistent with findings from two other studies of first episode mania patients we found statistically significant differences with moderate to large effect sizes between both patient groups and the healthy control group on measures of verbal recall, psychomotor speed, attention and some aspects of executive functioning as well as visuoconstructive reasoning. Psychomotor speed was the domain with the largest group differences. Eighteen percent of FM patients and sixteen percent of PM patients were

considered clinically significantly impaired across cognitive measures. Comparing the present findings to a non-overlapping sample of multiple-episode bipolar disorder patients from our study group suggests comparable dysfunction in some aspects of verbal recall and executive functioning, and consistently smaller deficits among the first-episode group on the remaining neuropsychological measures.

Studies of social functioning in patients who have recently been hospitalized for a first manic episode have found that about half of this group experience social dysfunction even after remission of clinical symptoms. When planning this thesis, there were no previous studies that had examined the relationship between neurocognition and social functioning in first episode mania. The third aim of the study was therefore to investigate both self-rated and clinician-rated social functioning in first-episode mania, and the relationship between social functioning and neurocognition. We found that compared to a matched healthy control sample, patients with first-episode mania displayed statistically significantly poorer self-rated social functioning on all subscales of the Social Functioning Scale. In addition, patients with previous untreated manic episodes rated themselves as being less competent in performing independent living skills, participated less in social activities, were less likely to be engaged in full-time employment and had a lower overall SFS score compared to patients with a first manic episode. There was also a relationship between a number of clinical measures and both self- and clinician-rated social functioning in the combined patient group. Depressive symptoms and processing speed had an independent contribution to self-rated social functioning, while psychotic symptoms significantly influenced clinician-rated social functioning.

These findings suggest that neurocognitive dysfunction is present early in the course of bipolar disorder and reaches the level of clinical significance in a subgroup of individuals. Comparing our results with multiple-episode patients, the findings also suggest that the neurocognitive dysfunction may increase with illness progression. Results also show that impairment of social functioning in BD is present already after a first manic episode, and is associated with a number of clinical variables although depression had the largest influence on self-rated social functioning. Neurocognition, except from processing speed, did not appear to play a significant role in social functioning at this stage. Still, the findings underline

the importance of assessing neurocognitive functioning in patients with bipolar disorder early in the illness course, and suggest that at least a subgroup of patients might benefit from treatment aimed at enhancing cognitive functioning. As depressive symptoms were strongly related to social functioning, complete functional recovery after a depressive episode should therefore be the goal of treatment as well.

ABBREVIATIONS

BD	Bipolar Disorder
BD I	Bipolar Disorder type I
BD II	Bipolar Disorder type II
BD NOS	Bipolar Disorder Not Otherwise Specified
CDS	Collaborative Depression Study
CVLT-II	California Verbal Learning Test – II
D-KEFS	Delis-Kaplan Executive Function System
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
FM	First Manic episode
GAF	Global Assessment of Functioning
GAF-F	Global Assessment of Functioning – Function scale
GAF-S	Global Assessment of Functioning – Symptom scale
GAS	Global Assessment Scale
HC	Healthy Controls
ICC	Intraclass Correlation Coefficients
IDS-C	Inventory of Depressive Symptoms – Clinician rated
IQ	Intelligence Quotient
MANOVA	Multivariate Analysis of Variance
MANCOVA	Multivariate Analysis of Covariance

MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MRI	Magnetic Resonance Imaging
NART	National Adult reading Test
NCS-R	National Comorbidity Survey Replication
NIMH	National Institute of Mental Health
PANSS	Positive And Negative Syndrome Scale
PAS	Premorbid Adjustment Scale
PM	Previous Manic episodes
PRIME-MD	Primary Care Evaluation of Mental Disorders
QoL	Quality of Life
SCID-I	Structured Clinical Interview for DSM-IV Axis I disorders
SFS	Social Functioning Scale
SPSS	Statistical Package for the Social Sciences
SS	Scaled Score
STOP-EM	Systematic Treatment Optimization Program for Early Mania
SZ	Schizophrenia
TOP	Tematisk Område Psykose (Thematically Organized Psychosis research)
UCLA	University of California, Los Angeles
YMRS	Young Mania Rating Scale
WAIS-III	Wechsler Adult Intelligence Scale-III
WASI	Wechsler Abbreviated Scale of Intelligence

1. INTRODUCTION

The essential feature of bipolar disorder (BD) is a clinical course that is characterized by periods of elevated mood and periods of depressed mood, in between periods of normal mood (euthymia). It is a severe mental illness that cause significant suffering and impaired functioning for the individuals affected by the disorder. Historically, mania and depression were first described by the ancient Greeks, but it was not until 1899 the term *manic-depressive insanity* was used by Emil Kraepelin. Kraepelin segregated the two illnesses – manic depressive insanity (bipolar disorder) and dementia praecox (schizophrenia) – from another, placing special emphasis on the features of manic depressive insanity that differented it from dementia praecox; the periodic or episodic course, the more benign prognosis and a family history of manic-depressive insanity (Goodwin & Jamison, 2007). The description of a relatively good outcome in BD may have led to the expectation that patients with BD should have a rather normal functioning between episodes. As more research on neurocognition and social functioning in BD has been carried out during the last decade, there is now an increasing opinion that patients with BD experience a great deal of social and cognitive dysfunction also between illness episodes. Attempts to understand the brain's role in BD began in earnest as clinically effective mood-altering drugs began to appear in the late 1950s and early 1960s. Over the next three decades, clinical studies attempted to uncover the biological factors mediating the pathophysiology of BD, including the measurement of neuropsychological functioning. Traditionally, the research on deficits in neurocognition and social functioning associated with BD has been following in the footsteps of schizophrenia research. A Pub Med search on the terms *cognition and bipolar disorder,* versus *cognition and schizophrenia,* and *social functioning and bipolar disorder,* versus *social functioning and schizophrenia,* displays nearly six times as many published articles on cognition in schizophrenia than in BD, and five times as many articles written about social functioning in schizophrenia compared to BD. The differences between first-episode studies in schizophrenia and BD are even larger. While there were 2007 articles published on *first*

episode schizophrenia, and 1663 articles published on *first episode psychosis,* only 320 articles on the search term *first episode bipolar disorder* were found in Pub Med. Studying first-episode BD patients may help us gain more knowledge about how the illness develops and progresses. It is for instance still uncertainty related to whether or not neurocognitive dysfunction in BD should be regarded as neurodevelopmental (i.e. born with) or neurodegenerative (i.e. progressive), and studies of patients early in the illness course might therefore facilitate to clarify some of the questions.

Although schizophrenia research has been somewhat ahead of BD research, internationally there has been an increasing amount of research on BD (see for instance Akiskal, 2002; Angst, 2008; Berk, et al., 2009). In Norway, a growing amount of research on BD throughout the latest decade have included numerous areas such as insight (Engh et al., 2007; Varga et al., 2006; 2007; 2009), substance abuse (Lagerberg et al., 2010a; 2011; Ringen et al., 2008), emotion perception (Aminoff et al., 2011; Vaskinn et al., 2007), age at onset (Larsson et al., 2010; Morken et al., 2009; Oedegaard et al., 2009), neurocognitive dysfunction in BDI and II (Andersson et al., 2008; Simonsen et al., 2008), genetics (Athanasiu et al., 2011; Djurovic et al., 2010; Kähler et al., 2010; Oedegaard et al., 2010; Tesli et al., 2009), MRI (Hartberg et al., 2011) and social functioning (Simonsen et al., 2011). However, less is known about the early stages of BD, including neurocognitive functioning and social functioning. As a part of the ongoing translational research project *Thematically Organized Psychosis research* (TOP), this thesis have investigated neurocognitive functioning and social functioning in first-episode BD compared to healthy controls. The relationship between neurocognition and social functioning, and with clinical characteristics of the group have also been explored.

Before describing the study that this thesis is based on, a brief description of DSM-IV bipolar I disorder (BD I) will be presented, along with a short description of neurocognition and psychosocial functioning in BD in general and in its early stages in particular. Some questions that needed answering at the planning of this thesis will also be discussed.

1.1. Clinical description of BD

In the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994) BD is subgrouped into BD I, BD II, Cyclothymia and BD NOS. A BD I diagnosis may be given on the basis of manic episodes only, while in BD II, at least one hypomanic episode and one major depressive episode are required to fulfill diagnostic criteria. BD type I will be the focus of the present thesis.

The DSM-IV main criterion for BD I is at least one manic episode that meet the following criteria: a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary). During the period of mood disturbance, at least three of the following symptoms should be present: inflated self-esteem or grandiosity; decreased need for sleep; being more talkative than usual or pressure to keep talking; flight of ideas or a subjective experience of racing thoughts; distractability; increase in goal-directed activity or psychomotor agitation; and/or excessive involvement in pleasurable activities that have a high potential for painful consequences. Mood symptoms also have to cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Psychosis can occur in both manic and depressed states in BD I. In a review of 33 studies, Goodwin and Jamison (2007) concluded that approximately two-thirds of patients with BD had a lifetime history of at least one psychotic symptom, more often during manic episodes. In a manic episode, grandiose delusions are the most common type of psychotic symptom, but any kind of psychotic symptom including thought disorder, hallucinations, mood-incongruent psychotic symptoms and catatonia can present as part of an episode (Dunayevich and Keck, 2000).

The lifetime prevalence rates of BD across countries ranges from 0.3 to 1.5 % (Weissman et al., 1996). Sherazi et al (2006) reviewed 18 studies and found a prevalence of BD I ranging from 0.1 to 1.8 %, however they suggest that studies may have overestimated prevalence of mania and underestimated incidence, and that incidence of mania may be increasing in later generations. In Norway, a large-scale psychiatric epidemiologic study of Oslo reported the

lifetime prevalence for BD to be 1.6% with an annual prevalence of 0.9% (Kringlen et al., 2001).

1.1.1. The early phases of BD

There has been a paucity of studies on early phases of BD, especially compared to the growing interest devoted to the early phase of other severe mental illnesses such as schizophrenia. Studies have provided considerable support for the importance of stressful life events in the onset of episodes (Hunt et al., 1992; Johnson and Miller, 1997) and the influence of life events triggering mood episodes is allegedly more prominent in earlier than in later phases of BD. The prodromal phase of BD before a first episode onset may be characterized by high levels of stress, suicide attempts, anxiety disorders and alchohol or substance abuse (Azorin et al., 2011; Winokur et al., 1998).

Data from 15 studies published after 1990 have reported an average age at onset of 22.2 years for BD (Goodwin and Jamison, 2007). Results from the TOP study group reported a mean onset at age 22.8, with 38% of BD patients having an early onset before age 18 (Larsson et al., 2010). Earlier onset of BD may be an important predictor of a more severe clinical course and poorer outcome (Carlson et al., 2000).

Both the detection and treatment of BD is often delayed. Berk and colleagues (2007) reported a median age of 24 at first medical treatment, but the correct diagnosis of BD was not achieved until patients were 30 years. A treatment delay of nearly nine to ten years has also been reported (Altamura et al., 2010; Goldberg and Ernst, 2002). Since about half of BD patients may experience one or more major depressive episodes before their first episode of opposite polarity (Perugi et al., 2000) it is not possible to diagnose BD correctly until they develop the first manic or hypomanic episode. Manic episodes may also often be atypical, mixed or dysphoric during adolescence or early adulthood (Berk et al., 2007) which makes recognition of manic episodes even more challenging. The future of early intervention in BD depends thus on a correct identification of individuals at risk for developing BD, and the

capacity to provide targeted treatment that specifically prevents onset or recurrence of episodes (Salvadore et al., 2009). Early initiation of appropriate therapy is important not only to improve clinical outcome but also to prevent sequela of untreated illness including negative impacts on family relationships, psychosexual and vocational development, identity and a concept of self (Berk et al., 2009).

The term *first contact mania* will be used in this thesis to describe the clinical sample, but other terms such as *first episode BD* and *first manic episode* will also be used interchangeably to describe patients in their early stages of the disorder.

1.2. Neurocognition in BD

Neurocognition is a term that is used in BD research amongst others, for what is traditionally called neuropsychology or cognition. *Neuropsychological function* is a term used to describe cognitive function in clinical groups, and covers a range of central cognitive functions or domains such as general intellectual functioning, attention, psychomotor speed, learning, memory and executive function. The contribution of traditional neuropsychological testing to our understanding of BD pertain several issues. Firstly, to provide an empirical basis for and clarification of clinical phenomenological concepts. Secondly, to determine which abnormalities are state dependent and which are state independent. Thirdly, to characterize the neuropsychological functions that appear to be most persistently impaired, providing a clue to pathophysiology. Finally, to determine the burden of the illness and its treatment with respect to cognitive functioning in terms of both cross-sectional and longitudinal outcomes.

Meta-studies of neurocognition in BD have demonstrated deficits on standardized neuropsychological measures within domains involving executive functioning, verbal learning and memory, attention and processing speed (Bora et al., 2009; Jamrozinski, 2010; Kurtz and Gerraty, 2009; Robinson et al., 2006; Torres et al., 2007;). A number of studies emphasize the role of mediating factors for cognitive functioning in BD, for instance, how neurocognitive impairment is associated with clinical factors related to the illness. Number of episodes suffered (El-Badri et al., 2001), the number of hospital admissions (Martinez-

Aran et al., 2004; Rubinsztein et al., 2000; Thompson et al., 2005) and duration of illness (Cavanagh et al., 2002; Clark et al., 2002; Martinez-Aran et al., 2004; Thompson et al., 2005), alcohol abuse (Holmes et al., 2009; Sanchez-Moreno et al., 2009), depressive symptoms (Malhi et al., 2004), manic symptoms (Strakowski et al., 2010) and history of psychosis (Simonsen et al., 2011) have all been related to neurocognitive impairment. The effect of antipsychotic medication on neurocognitive functioning may also be significant (Dittmann et al., 2008; Jamrozinski et al., 2009), particularly polypharmacy (Balanza-Martinez et al., 2010). However, a number of meta-analysis report neurocognitive deficits in individuals with BD also during euthymic states (Bora et al., 2009; Robinson et al., 2006; Torres et al., 2007), which challenges the former idea that impairment is transient and limited to the acute phases of the illness.

The majority of studies have focused on the average neurocognitive performance of a BD group compared to a healthy control group, but fewer have investigated how many individuals with BD have so called clinically significant cognitive impairment, i.e. impairments that are so severe that one would expect it to have an impact on everyday life. The proportion of patients that have clinically significant cognitive impairment is variable, and depends on the particular task employed. Studies have reported clinically significant impairment (i.e. $\leq$ 1.5 SD below control group mean or scoring below the 5th percentile, respectively) varying from 3-36% (Simonsen et al., 2008) and 3.2-41.9% (Thompson et al., 2005), suggesting that more than half of people with BD do not experience cognitive difficulties or experience it only at a subclinical level.

The etiology of cognitive dysfunction in BD is probably multifactorial, including gene-environment interactions (Balanza-Martinez et al., 2010). A number of neurocognitive domains have been suggested as cognitive *endophenotypes* for BD. Endophenotypes should be associated with illness, they should be heritable and they should co-segregate within families with the illness (Bora et al., 2009). Studies of relatives to patients with BD have found deficits in verbal learning/memory, working memory (Balanza-Martinez et al., 2008) as well as response inhibition deficits (Bora et al., 2008) and these deficits are thus suggested as possible endophenotypes for BD. Findings from schizophrenia research indicate that processing speed deficits also may be central to several mental disorders (Dickinson et

al., 2007). Impairments in working memory and verbal learning has been linked to processing speed in schizophrenia (Leeson et al., 2010) and bipolar disorder (Kieseppä et al., 2005) which adds to a growing body of research demonstrating the importance of processing speed for cognitive functioning and clinical outcome in severe mental disorders.

The available MRI literature indicates that specific structural brain abnormalities are already present around the time of illness onset (Vita et al., 2009), and also in unaffected family members of patients with BD (Hajek et al., 2005). A number of MRI studies on first episode BD have demonstrated a pattern of brain abnormalities similar to the most replicated findings detected in samples of chronic patients, that is, enlargement of the ventricular system (Strakowski et al., 1993), smaller area of the corpus callosum (Atmaca et al., 2007), and the presence of brain white matter hyperintensities (Zanetti et al., 2008). Other MRI studies have reported significantly different cortical and subcortical brain abnormalities at illness onset that are not detected consistently in chronic patients, such as decreased volumes of frontal lobe and temporal gyrus gray matter (Farrow et al., 2005), reduction in neocortical (Nakamura et al., 2007) and cingulated gyrus (Farrow et al., 2005; Yatham et al., 2007) gray matter volume, smaller amygdala volume (Rosso et al., 2007), and larger than normal striatum (Strakowski et al., 2002). These findings support the hypothesis of different changes in brain morphology over the time course of BD.

Evidence for progressive cognitive decline in BD is still inconclusive. There is however some agreement that a neurodegenerative model may be appropriate for deficits in at least some cognitive domains (Goodwin et al., 2008). Whether the neurocognitive deficits reflects a widespread dysfunction or is a consequence of a primary deficit in a core cognitive functioning is unknown.

1.2.1. Neurocognitive functioning in first-episode BD

Although studies of neurocognition in first episode BD are few, their results suggest that neurocognitive deficits is present early in the course of the disorder. Studies comparing first-episode BD patients to schizophrenia spectrum first-episode psychosis patients have either found less severe cognitive dysfunction in BD (Hill et al., 2009; Zanelli et al., 2010) or no clear

group differences (Barett et al., 2009; Zabala et al., 2010). Executive dysfunction in first-episode BD compared to healthy controls has been reported in two studies (Fleck et al., 2008; Gruber et al., 2008).

A study from 2006 assessing neurocognition in 16 euthymic BD I patients who had recently received in- or outpatient treatment for a first manic episode, compared to 30 multiple-episode BD I patients, found that the performance of the first-episode patients were significantly worse than the multiple-episode patients on tests of executive functions, sustained attention and perceptuomotor function (Nehra et al., 2006). The finding is somewhat contrary to expectations, but may be due to differences in demographic variables between the two groups, as patients in the first-episode group had for instance more psychotic symptoms and less education than the multiple-episode group. Torres et al (2010) reported moderate effect size differences between 45 euthymic BD I participants who had recently experienced their first manic episode compared to healthy comparison subjects on tasks assessing multiple cognitive domains, including sustained attention, learning and memory, and nonverbal/spatial reasoning. The percentage of patients showing cognitive impairment (i.e. scoring more than 1.5 SD below the mean of the control group) ranged from 11-31% (Torres et al., 2010). When comparing the data to previously published meta-studies of multiple-episode euthymic BD samples (Robinson, 2006; Torres, 2007) results demonstrated that the magnitude of cognitive impairment in first-episode BD might be comparable to multiple-episode BD on tasks that included premorbid/verbal intellectual ability and attention/processing speed.

1.3. Social functioning in BD

The term social/psychosocial functioning is here used to cover functioning in different aspects of daily living. In schizophrenia research, *functional outcome* is a more frequently used overall term for the above aspects of daily living (Green, 2006). The more general terms of psychosocial functioning, functional outcome and functioning will to some extent be used interchangeably in this thesis. Functioning is a complex term but will for the most

part involve different domains such as the capacity to work or study, the capacity to live independently, the capacity for recreation, and the capacity for romantic life (Zarate et al., 2000). There are many different ways to measure social functioning, and the field has been disadvantaged by the use of a multitude of different assessment instruments that vary in their capacity to capture the heterogeneity of this area. In their review, Burns and Patrick (2007) found that the most frequently used social functioning scales in the assessment of schizophrenia were the Global Assessment of Function (GAF; American Psychiatric Association, 1994), the Global Assessment Scale (GAS; Endicott et al., 1976) and the Social Functioning Scale (SFS; Birchwood et al., 1990), respectively. Measurement of psychosocial outcome, particularly self-report assessment, have been controversial in the psychiatric literature (Smith et al., 1997) as patients' illnesses might distort their abilities to self-report.

Although Kraepelin described a relatively good outcome of manic-depressive illness (Kraepelin, 1921), it has subsequently been recognized that some patients with BD experience a poor outcome. In fact, BD has been associated with significant impairment in work, family and social life, beyond the acute phases of the illness (Sanchez-Moreno et al., 2009). In a review from 2001 (MacQueen et al., 2001) between 30-60% out of 1450 patients with BD had detectable levels of social impairment, with impairments occurring in both occupational and social realms. BD has a negative effect on employment and productivity at work. A report from the National Comorbidity Survey Replication (NCS-R) based on 3.378 workers in the US (Kessler and Merikangas, 2004) revealed that bipolar disorder was associated with 65.5 lost workdays per ill worker per year, which was substantially more than in major depressive disorder (27.2 lost workdays per ill worker per year) (Kessler et al., 2006). The National Institute of Mental Health Collaborative Depression Study (NIMH-CDS) assessed 158 patients with BD I during 15 years and found that they were completely unable to carry out work role functions during 30% of the assessed months including symptom-free (euthymic) periods, which was significantly more than for unipolar major depressive disorder or BD II comparison subjects (Judd et al., 2008). In every country where statistics are available, the percentage of unemployed persons with BD is significantly above the mean level of unemployment (Morselli et al., 2004). One Norwegian study that investigated the relationship between length of education and social and occupational functioning in BD, found that BD patients had the same level of education but significantly lower social and

occupational function than the general population, and that BD was significantly associated with single status, low annual income and being on disability pension (Schoeyen et al., 2010).

Studies of patients with BD have found a gap between syndromal recovery (i.e. no longer meeting the criteria for an ongoing DSM illness episode) and functional recovery. A large prospective study of remission and functional recovery in 1656 patients with BD I reported that functional recovery occurred in approximately half of those who achieved remission after 2 years (Haro et al., 2010). Studies of patients hospitalized for a first manic episode have found similar results. Keck, McElroy, Strakowski et al (1998) found that although syndromal recovery occurred in 48% of patients hospitalized for a first manic or mixed episode of BD, functional recovery occurred in only 24% of patients. The McLean/Harvard first-episode mania project found that functional recovery by six- and twenty-four months was nearly three times less likely than syndromal recovery; and 63 % of those recovering syndromally did not recover functionally by 2 years (Tohen et al., 2000). A prospective study from the Systematic Treatment Optimization Program for Early Mania (STOP-EM) showed that within 6 months of a first manic episode, 88.6% of patients had met criteria for remission of manic symptoms, but 25.7% showed at least moderate disability of functioning (Kauer-Sant'Anna et al., 2009).

The most common clinical factors associated with impaired social functioning are related to depressive- or subsyndromal depressive symptoms (Bonnin et al., 2010; Fagiolini et al., 2005; Kauer-Sant'Anna, Bond, Lam, & Yatham, 2009; Martino et al., 2009; Mur et al., 2009; Pope, Dudley, & Scott, 2007; Simon et al., 2007). Episodes of depression have been associated with greater impairment in work, family and social life than episodes of mania (Calabrese et al., 2004; Rosa et al., 2010). Poor functional outcome in BD has also been associated with a number of other clinical factors such as psychosis (Tohen et al., 1992), number of past episodes (MacQueen et al., 2000), hospitalizations (Ozer et al., 2002; Strakowski et al., 1998) and age at onset (Meeks, 1999; Perlis et al., 2009; Tsai et al., 2001), amongst others.

One important question is whether or not the psychosocial functioning in BD becomes impaired after onset of the first episode, or if there are signs of poor functioning already before this. In schizophrenia, retrospective studies has shown poor premorbid adjustment among patients who later developed the disorder (Larsen et al., 1996). Cannon

et al (1997) reported that adult-onset BD patients had significantly poorer overall and adolescent premorbid adjustment than normal controls and that they did not differ from a schizophrenia comparison group on sociability. However a later study could not confirm this finding (Uzelac et al., 2006). Goldberg and Ernst (2004) found that poor premorbid adjustment during childhood or adolescence tended to be related to co-occurring alcohol and substance abuse and an increased risk of suicide attempts in adult BD patients.

1.4. The relationship between neurocognition and social functioning in BD

Although clinical symptoms have been found to affect social functioning, several studies have also reported various areas of neurocognitive functioning to be independent correlates of social functioning. Neurocognition has been found to be significantly associated with psychosocial functioning in 6 of 8 studies of euthymic BD participants, and in 5 of 5 studies of non-euthymic BD samples (Wingo, Harvey, & Baldessarini, 2009). Various areas of neurocognition such as verbal memory (Altshuler et al., 2008; Bonnin et al., 2010; Martinez-Aran et al., 2007; Martino et al., 2009), attention (Martino et al., 2009), executive functioning (Altshuler et al., 2008; Bonnin et al., 2010; Martinez-Aran et al., 2007; Martino et al., 2009) and processing speed (Mur et al., 2009) are all linked to social functioning, and have also been reported to predict long-term functional outcome in BD patients. Soft neurological signs (especially frontal signs) have also been reported to correlate strongly with social functioning (Goswami et al., 2006). Cognitive abilities including memory, planning or problem solving strategies and the emotional processing of information or social cognition are probably needed to cope satisfactory with the different psychosocial situations, and difficulty remembering long-term information may represent a serious problem for BD patients in their occupational functioning as well as in their interpersonal relationships (Sancez-Moreno et al., 2009).

Studies concerning the relationship between neurocognition and social functioning in first-episode BD patients are few. Torres et al (2010) studied the impact of cognitive functioning on longitudinal 6-month functional and clinical outcome in 45 (of 53) recently diagnosed clinically stable patients with BD I. Memory, particularly verbal learning/memory, was

robustly associated with 6-month functional outcome on a functioning scale, even after partialling out the influence of mood symptoms and substance abuse co-morbidity. There was however, a surprising lack of association between baseline cognitive functioning and concurrent baseline psychosocial functioning.

1.5. Unanswered questions

When the work on this thesis started out, there was little research on neurocognitive functioning in the early stages of bipolar disorder, although some studies with small samples had reported neurocognitive dysfunction early in the illness course. Questions that needed further investigation were for instance: do first-episode BD patients have specific or general cognitive deficits, are the deficits comparable to those found in multiple-episode BD patients, and how many patients have *clinically significant* cognitive impairment?

The possible relationship between clinical characteristics, neurocognition and social functioning had up until then not been investigated in first manic episode BD. At present, there is still only one published study that examines the relationship between neurocognition and social functioning in first-episode BD. There was therefore a need to investigate this relationship further in a sample of patients with first-episode mania.

One of the study's aims was to investigate social functioning using a rating-scale that captured several aspects of social functioning. In order to achieve this, the Social Functioning Scale needed to be validated in its Norwegian version. Premorbid functioning and the relationship with current social functioning also needed investigation.

Finally, since the *first contact* mania group was divided into two subgroups based on the number of previous manic episodes, possible group differences in neurocognition and/or in social functioning would also be of interest for this thesis.

2. AIMS OF THE THESIS

Paper I

Paper I had three aims: Firstly, to establish the reliability and validity of the Norwegian version of the Social Functioning Scale (SFS), and secondly, to investigate if the scale, originally developed for patients with schizophrenia, could be used for patients with bipolar disorder and healthy control subjects. Finally, the last aim was to examine social functioning in patients with bipolar disorder compared to patients with schizophrenia and healthy control subjects.

Paper II

The first aim of paper II was to describe neurocognitive functioning in the two BD subgroups (FM and PM) compared to an age, gender and education matched sample of healthy control participants, with a particular emphasis on the magnitude of cognitive deficits and number of clinically impaired cases within the cognitive domains. In addition we aimed to investigate if group differences could be explained by impaired processing speed. The second and specific aim of the paper was to examine if cognitive impairments were related to premorbid- and early illness characteristics, in particular age at onset, duration of untreated illness and number of episodes (manic, depressive and psychotic) prior to first treatment for BD. This might be helpful to the understanding of neurocognitive dysfunction in BD as trait- or state related, or a combination of both.

Paper III

The aims of paper III was firstly, to provide a comprehensive characterization of social functioning in the two BD subgroups (FM and PM) compared to healthy controls, using both clinician-rated and self-report measures. The second aim was to examine the relationship

between current self-reported and clinician-rated social functioning and neurocognition, age at onset, premorbid adjustment and clinical symptoms.

3. METHODS

3.1. Setting

The present study is a naturalistic, cross-sectional study of patients coming to their first treatment for a manic episode (*first contact* mania), conducted within the framework of the Thematically Organized Psychosis (TOP) study group and the Regional Psychosis Research Network. The TOP study is a large, ongoing translational research study with the main aim of investigating clinical and biological characteristics of psychotic disorders to gain more knowledge about the pathophysiological mechanisms related to clinical, biological and environmental aspects of BD, schizophrenia and related psychotic disorders. The study group is affiliated with the University of Oslo, Oslo University Hospital (Ullevål University Hospital, Rikshospitalet, Aker University Hospital), Lovisenberg – Diakonhjemmet hospital and through the regional network to two large hospitals outside of Oslo (Innlandet Hospital and Akershus University Hospital).

Patient inclusion to the TOP study started in October 2002, and is still ongoing, recruiting patients within diagnostic groups that are being treated in the psychiatric services at the participating hospitals. The study's clinical assessment team involved in patient inclusion collaborates closely with the clinical staff in the psychiatric units. The Norwegian mental health care system has a catchment area patient admittance system, which offers public mental health care to all individuals with mental illness within a given catchment area, resulting in a relatively high degree of representativity for study participants. Healthy control participants were randomly selected from national statistical records from the same catchment area and contacted by letter inviting them to participate.

The study is approved by the Regional Committee for Medical Ethics, Norwegian Data Inspectorate. The data file received an Audit Certificate from the Center for Clinical Research at Ullevål University Hospital in 2007.

Participants gave written informed consent to enter the study after receiving a complete description of the study.

3.2. Participants

Patients included in the current thesis were recruited from the psychiatric units (in- and outpatient) of the three major hospitals in Oslo and from Akershus University Hospital in the period of 2002 – 2010. This study uses two different samples. The samples used in paper II and III are identical, and differs from the sample used in study I.

Table I: Total number of participants across papers

	First contact mania (PM + FM)	Bipolar spectrum disorders	Schizophrenia spectrum disorders	Healthy controls	Data collection
Paper 1	--	100	100	100	October 2002 – September 2008
Paper 2	55	--	--	110	May 2006 – June 2010
Paper 3	55	--	--	110	May 2006 – June 2010

Table II: Demographical and clinical data of the samples used in paper 1, 2 and 3

	First contact mania		Chronic patients		Healthy controls	
	First manic episode (FM)	Previous manic episodes (PM)	Bipolar spectrum disorders	Schizophrenia spectrum disorders	HC Paper 1	HC Paper 2 & 3
Age, mean (SD)	31.2 (9.6)	30.5 (10.6)	37.1 (12.6)	31.3 (9.4)	32.0 (9.2)	31.1 (9.8)
Sex, n male/female	15/19	8/13	45/55	52/48	52/48	49/61
Years of education mean (SD)	13.1 (2.2)	12.9 (2.3)	13.6 (2.4)	12.1 (2.3)	14.1 (2.1)	13.4 (1.9)
WASI full-scale IQ, mean (SD)	108.6 (14.7)	106.9 (9.6)	106.5 (11.1)	96.6 (16.1)	114.4 (9.6)	111.6 (11.4)
PANSS-P, mean (SD)	11.6 (5.5)	11.5 (3.8)	10.0 (3.5)	15.9 (5.3)	--	--
PANSS-N, mean (SD)	9.6 (3.0)	9.7 (3.8)	10.2 (4.0)	16.1 (6.8)	--	--
GAF-F, mean (SD)	54.5 (15.3)	50.1(11.0)	54.7 (11.5)	42.4 (10.7)	--	--
GAF-S, mean (SD)	47.7 (11.2)	48.9 (11.2)	57.1 (11.1)	41.2 (10.3)	--	--

In paper 1 two diagnostic groups were defined. The bipolar spectrum disorder group consisted of BD type I (62%), BD type II (30%) and BD not otherwise specified (6%). The schizophrenia spectrum group consisted of schizophrenia (74%), schizoaffective disorder (12%) and schizophreniform disorder (16%).

The samples in paper 2 and 3 consisted of a total of 55 BD participants with a first contact manic episode. Patients were defined as first episode BD if they met the diagnostic criteria for DSM-IV BD I disorder and were receiving their first adequate treatment for a manic or mixed episode. Patients could have experienced previously untreated manic episodes, or have received treatment for a major depressive episode and still be included in the study. Since acutely manic patients are not always able to give informed consent, patients identified as first contact mania were included up to one year after start of first treatment. The cohort was divided into two groups according to their number of previous manic episodes. The first group; First Manic episode (FM; n=34), had only had one single manic episode lifetime (the current). The second group; Previous Manic episodes (PM; n=21), had experienced previous manic episodes although those episodes had neither been identified as manic episodes at the time, nor being adequately treated as such.

Exclusion criteria for all participants were: history of head injury with neurological complications, neurological disorder, unstable medical condition that interferes with brain function, mental retardation (IQ < 70) and being unable to comprehend the Norwegian language at an acceptable level. In paper 2 and 3 participants needed to have Norwegian as their first language or having received their compulsory schooling in Norway, and had to score 15 or above on the forced recognition trial in the California Verbal Learning Test (CVLT-II) (Delis et al., 2004). In order to assure a healthy control sample the control participants in all three studies were screened with the Primary Care Evaluation of Mental Disorders (PRIME-MD; Spitzer et al., 1999) and were excluded if they or any close relatives had a lifetime history of a severe psychiatric disorder (schizophrenia, bipolar disorder or major depression), or if they had substance abuse or dependency the last 6 months.

3.3. Measures

3.3.1. Clinical assessment

Diagnosis was based on the Structured Clinical Interview (SCID) for DSM-IV, modules A-E (First et al., 1995). All interviewers were trained based on the training program at UCLA (CA, USA), were given regular individual supervision of assessments by senior research personnel and participated in regular diagnosis consensus meetings. Diagnosis reliability was found satisfactory with agreement for DSM-IV diagnostic categories with an overall kappa score of 0.77 (95% CI: 0.60-0.94)[1].

The level of current symptomatology was defined based on the following scales: Current depressive symptoms were rated using the Inventory of Depressive Symptoms-Clinician rating (IDS-C) (Rush et al., 1986). Current manic symptoms were rated using the Young Mania Rating Scale (YMRS) (Young et al.,1978). Current positive and negative symptoms were rated using the Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1987). Inter-rater reliability for the PANSS was acceptable with intraclass correlation coefficients (ICC) of 0.73 (95% CI: 0.54-0.90).

Current overall degree of present symptoms was assessed with the split version of the Global Assessment of Functioning – symptom level (GAF-S; Pedersen et al., 2007). The split version of the GAF separates symptom and function into two different scores, the GAF-Symptom level and the GAF-Function level (GAF-F). Here, GAF-S represents overall degree of symptoms. GAF-F, global clinician-rated social functioning, will be discussed in further detail in the next section. Inter-rater reliability for GAF-F and S was satisfactory, with an ICC of 0.86 (95% CI: 0.77-0.92).

Data on age, gender, ethnicity, marital status, education, occupational status, family history of psychiatric disorders including substance abuse, history of suicide attempts, history of psychosis, psychiatric hospitalizations and psychopharmacological treatment, age at onset of

[1] The following reliability ratings apply for the total clinical sample used in paper 1, and partially the clinical sample used in paper 2 and 3.

affective episodes and age at first contact with specialized psychiatric care were also collected. The information was confirmed using medical charts and interviews with close family members if relevant.

Patients were considered to have had a lifetime psychotic episode if they had one or more SCID-verified psychotic episode. Current psychosis was defined as a score of 4 or higher on any of the following PANSS items: P1, P3, P5, P6 and G9.

Each patient reported lifetime substance use (daily, weekly, monthly or occasional/no use) for all substances including alcohol, amphetamine, cocaine, cannabis, ecstasy, heroin/ other opiates, hallucinogens, solvents and prescription drugs for the following life periods: 11-15 years, 16-20 years, 21-27 years, 28-44 years, 45-60 years and 60+ years. The lifetime substance use evaluation is administered as an interview, where the scores are based on the clinician's evaluation of the patients' reports.

3.3.2. Assessment of current and premorbid social functioning

Social functioning was assessed with a self-rating scale and a clinician-rating scale. The Social Functioning Scale (SFS; Birchwood et al., 1990) was developed to measure different areas of functioning that are crucial to the community living of individuals with schizophrenia. The scale was designed with two requirements in mind: (1) to provide a detailed assessment of patients' strengths and weaknesses, both to guide an intervention and to provide the clinician with possible specific goals, and (2) the ability to synthesize such detailed reporting into coherent, reliable scales (Birchwood et al., 1990). The Norwegian version of the SFS was translated in 2003 by members of the TOP study group; Anja Vaskinn and Kjetil Sundet, and back-translated to English by a bilingual research fellow; Torill Ueland. It has been accepted as the official Norwegian version by the British developers (PROQOLID, 2007). The Norwegian version of the SFS has been used in several projects (Simonsen, Sundet, Vaskinn et al., 2010; Vaskinn, Sundet, Friis et al., 2008a, 2008b; Øie, Sundet & Ueland, 2011). The SFS is constructed to measure social skills and performance among patients with schizophrenia, and is a self-administered questionnaire consisting of 76 items sorted into seven subscales as the sum of all items within each area. Each subscale is standardized and normalized to a

scaled score (SS) with a mean of 100 and a standard deviation of 15, based on a sample of 334 outpatients with schizophrenia (Birchwood et al., 1990). The SFS total score is calculated by adding all seven subscale SSs and dividing the sum on the number of subscales (=7). The SFS enumerates key skills and social behaviors which informants record as present or absent. Items are rated on a four-point scale of frequency or ability; with a higher score indicating a higher frequency or more competent behavior. The SFS also distinguishes lack of competence from lack of performance: lack of competence refers to the absence or loss of a skill, while lack of performance refers to non-use of an available skill. The seven subscales are:

(1) Withdrawal (time spent alone, initiation of conversation, social avoidance)

(2) Interpersonal behavior (number of friends, having a romantic partner, quality of communication)

(3) Pro-social activities (engagement in a range of common social activities, e.g. going to the cinema)

(4) Recreation (engagement in a range of common hobbies and interests)

(5) Independence-competence (the ability to perform skills necessary for independent living, like shopping for groceries, doing laundry etc.)

(6) Independence-performance (the actual performance of those same skills)

(7) Employment (engagement in productive employment or a structured program of daily activity)

The GAF-Function level scale (GAF-F; Pedersen et al., 2007) was used to measure clinician-rated social functioning. GAF is a clinician-rated scale with scores based on all available information. The original GAF scale is a further development of the Global Assessment Scale (GAS; Endicott et al., 1976) and was introduced as the axis V of the DSM-III-R in 1987. One of the benefits with the GAF scale is that it is not disorder-specific, but can be used across a wide range of mental disorders. Both GAF-F and GAF-S scales are rated from 1 to 100 with 100 representing the hypothetically best possible functioning and 1 representing the hypothetically lowest possible functioning. For the purpose of study 1 and 3 only the function part of the scale (GAF-F) was used as a measure of social functioning.

To measure premorbid social functioning the Premorbid Adjustment Scale (PAS) was used (Cannon-Spoor et al. 1982). The PAS is a rating scale designed to evaluate the level of functioning in four major areas at each of several periods of the subject's life: (1) social accessibility - isolation, (2) peer relationships, (3) ability to function outside the nuclear family, and (4) capacity to form intimate socio-sexual ties. Items evaluating age-appropriate functioning in these areas are repeated for each period of the subject's life. The four period sections are: Childhood, up to 11 years; Early Adolescence, 12-15 years, Late Adolescence, 16-18 years; and Adulthood, 19 years and beyond. Scores range from 0-6 where 0 represents the best possible functioning. The PAS was administered as part of the clinical assessment and was based on patients self-report. In the analyses, PAS scores were divided into two domains – Academic and Social – and for each domain we discriminated between level and change (Larsen et al. 2004). To measure initial level, we used the childhood scores for each domain, while change was calculated as the difference between the latest avilable score and the childhood level score.

3.3.3. Neurocognitive assessment

Neurocognitive assessment was carried out by psychologists trained in standardized neuropsychological testing. A three hour test battery was administered in a fixed order with two breaks in between. Test scores were initially calibrated across investigators in order to assure a common scoring technique. Measures included in this study are previously found sensitive to dysfunction in schizophrenia and bipolar spectrum disorders (Simonsen et al., 2008). Although assigning tests to one specific cognitive domain remains controversial, we assigned the tests to the following and more specific neurocognitive functions or domains:

Learning and memory

Using the Logical Memory test, part of the Wechsler Memory Scale (WMS-III) (Wechsler, 2007a), the total number of items immediately recalled from two short stories that each

were read once was used as a measure of verbal learning, while the total number of items freely recalled after 30 minutes was used to measure delayed verbal recall.

From the California Verbal Learning Task (CVLT-II) (Delis et al., 2004) we used the total number of words repeated immediately after five reading trials of a list of 16 words as a measure of verbal learning. The number of words freely recalled after 30 minutes was used to measure delayed verbal recall.

To assess visual memory we used the Rey-Osterrieth Complex figure test (Meyers & Meyers, 1995). Subjects were first asked to copy a complex figure onto a sheet of paper, and after a 30-minute time delay they were asked to draw the same figure from memory. Number of points earned was used to measure delayed visual recall.

Psychomotor speed

Grooved Pegboard (Klove, 1963) was used to assess fine motor speed. The task consists of a small board containing a set of 5x5 slotted holes angled in different directions, and small pegs that fits into the holes. Each peg has a ridge along one side, requiring it to be rotated into position for correct insertion. The subject is asked to fill pegs in all holes, and the score is time to completion. We used an average of right and left hand to calculate scores.

To assess psychomotor speed Digit Symbol-Coding, a part of the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 2003), was used. The test consists of a printed sheet with rows containing small blank squares each paired with a randomly assigned number from one to nine. Above these rows are a printed key that pairs each number with a different nonsense symbol. The subject must fill in the blank spaces with the symbol that is paired to the number above for 120 seconds. Number of spaced filled out correctly was used to measure psychomotor speed.

From the first trial in the Color-Word Interference Test, part of the Delis Kaplan Executive Functioning Scale (D-KEFS) (Delis et al., 2005), the color naming task was the time taken to name the color of different ink dots on a paper, and the second task, word reading, consisted of time taken to read words on a paper.

Attention

Attention was assessed using the Digit Span from the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 2003). The maximum number of digits repeated in the same order as presented (forward version) was used as a measure of focused attention and the maximum number of digits repeated in a backward order of appearance (backward version) was used as a measure of working memory.

In Letter-Number sequencing, also from WAIS-III, subjects hear lists of randomized numbers and letters of increasing lengths, and are asked to repeat numbers and letters from the lowest in each series, and numbers always first.

The Bergen *n*-back Test (N-back) (Haatveit et al., 2010) is a computer-based test requiring subjects to press a button every time two numbers displayed on the screen are the same as the numbers displayed two screen pictures back ('2-back'). The *d*' is calculated from hit-rate and false alarm rate using the formula $d' = Z_{HIT} - Z_{FA}$ where Z represents a transformation of the two distributions allowing for comparison of measures with different ranges of absolute values.

Executive function

Executive function was assessed using subtests from the D-KEFS battery (Delis et al., 2005). From the Verbal Fluency subtest, the number of words beginning with the letters 'F', 'A' and 'S' generated separately within 60 seconds was used as a measure of phonetic fluency. The number of animals' and boys' names generated separately within 60 seconds was used as a measure of semantic fluency. Finally, the number of fruit and furniture generated while alternating between the two categories was used as a measure of semantic set-shift.

From the third trial in the Color-Word Interference Test, also part of the D-KEFS (Delis et al., 2005), the time taken to name the color of the ink on a list of written names of colors that are incongruent with the color of the ink was used to measure interference control. From

the fourth trial, the time taken to complete the alternation between naming the color of the ink and naming the written word was included as a measure of interference set shift.

The Wisconsin Card Sorting Test (Kongs et al., 2000) is a computer-based task where the subject is asked to place cards with four different printed symbols – triangle, star, cross or circle – in red, green, yellow or blue, one by one under four stimulus cards on the screen. After each response the person will get a feedback on the screen whether the response was correct or not. The placement will be correct for a nontarget category as well as a target category such as matching both color and form. Perseverative responses occur when the subject continues to sort according to a previously successful principle or persists in sorting on the basis of an initial erroneous guess. Categories achieved refer to the number of correct runs of ten sorts.

IQ

Premorbid IQ was measured using the National Adult Reading Test (Nelson & Willison, 1991), Norwegian version (Sundet & Vaskinn, 2008).

The Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler et al., 2007b) consists of four tests; Vocabulary, Similarities, Block Design and Matrix Reasoning. On the Vocabulary task subjects are asked to explain the meaning of different words, in order of difficulty. In Similarities the subject must explain what each of a pair of words has in common. Block Design is a construction test where subjects are presented with red and white blocks and the task is to use the blocks to construct replicas of designs of increasing difficulty printed in a scale smaller than the blocks. In Matrix Reasoning the subject must choose from a multiple-choice array of visual patterns the item that best completes the pattern.

Clinically significant cognitive impairment

Neurocognitive dysfunction was investigated by comparing the mean performance for the different groups, however we were also interested in how many of the patients were

impaired to a degree that would be considered clinically significant. To assess cognitive impairment, the proportion of BD- and healthy control participants with clinically significant cognitive impairment, defined as neurocognitive scores 1.5 SD below the average of the healthy control group was calculated. Accordingly, the cut-off of 1.5 SD would also define 7% of the healthy control participants as impaired as it captures participants performing below the normative seventh percentile level.

3.4. Statistical analyses

All analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 16.0. Group comparisons of demographics, clinical characteristics, neurocognition and social functioning were carried out with a range of analyses. Group differences across continuous variables were investigated with t-tests, Mann-Whitney U tests or analyses of variance (ANOVA), while categorical variables were investigated with Chi-square analysis. Correlations between variables were explored by Spearman or Pearson rank correlations according to type of data. All tests were 2-tailed, and limits for significance was set to the 0.05- or 0.01 level, the latter due to multiple comparisons.

Reliability analyses in paper 1 was performed by reporting mean item-total correlations, mean inter-item correlations, and Chronbach's alpha for the seven subscale scores and full scale score. Pearson's product-moment correlations *(r)* between both the SFS full scale score and the seven subscale scores, and between the seven subscale scores was reported. Principal component analysis (with Varimax rotation when more than one component was indicated by Eigenvalues $\geq$ 1.0), was performed using the seven subscale scores, both for the total sample as well as within the SZ, BD and HC groups separately.

Effect sizes were reported by the squared eta-correlation (n^2) in all three papers, in addition to z-scores that were used in paper 2.

In paper 2, group differences of neuropsychological test performance was explored using between-subjects univariate ANOVA with effect size (eta squared) of group differences and

Scheffès post hoc tests. Bonferroni corrections were applied for all cognitive domains. Analysis of covariance (MANCOVAs) investigated if group differences in neurocognitive performance remained significant when psychomotor speed was controlled for by entering Digit Symbol Coding as covariate.

In paper 3, hierarchical multiple linear regression analyses with variables entered in blocks was carried out to explore the independent contribution of neurocognition and current symptomatology to self-rated (SFS) and clinician-rated (GAF-F) psychosocial function. We chose clinical and neurocognitive variables that correlated $\geq$ .20 with at least one of the functional measures in the bivariate analyses for the regression analyses. In the analyses clinical and premorbid variables were entered in block 1 and neurocognitive measures in block 2.

A thorough description of the statistical analyses used in the three studies, are given in the three papers.

4. SUMMARY OF PAPERS

Paper I: Validation of the Norwegian version of the Social Functioning Scale (SFS) for schizophrenia and bipolar disorder

Background: Studies of social functioning in severe mental disorders have been challenged by the multitude of different assessment instruments in use. The present study aims to establish reliability and validity of the Norwegian version of the Social Functioning Scale (SFS) and to examine social functioning in bipolar disorder (BD) compared to schizophrenia (SZ) and healthy controls (HC).

Methods: SFS, a 76 item questionnaire divided into seven subscales measuring various aspects of daily life functioning, was administered to samples diagnosed with BD (n = 100) or SZ (n = 100) and to HC subjects (n = 100), recruited from the ongoing Thematic Organized Psychosis research (TOP) study.

Results: Reliability analyses based on the three groups combined (n= 300) prove adequate psychometric properties both for the composite full scale score (alpha: 0.81) as well as for the seven subscale scores (alpha: 0.60-0.88). Principal component analysis of the subscale confirms a one-component structure, explaining 59% of the variance. Looking at the groups separately, a one-component solution was preferred for the BD group, while a two-component solution for the SZ group, and a three-component solution for the HC group was suggested.

Conclusion: Although significantly correlated with the Global Assessment of Functioning, our results indicate that the SFS measures different aspects of social functioning, is less influenced by demographic and clinical characteristics, but differentiates at the same time significantly patients with severe mental illness from healthy controls. The scale seems to work well for patients with BD. Thus, SFS adds valuable information as a supplement to

standard clinician-rated assessment tools of social functioning, suited for both research and clinical work.

Paper II: Neurocognitive functioning in patients recently diagnosed with bipolar disorder

Background: Cognitive dysfunction in bipolar disorder is well established in the literature; however, there are few studies of neurocognition in patients early in the course of the illness. In the present report, we describe neurocognitive function in a first contact mania sample – separated into two groups based on the number of previous untreated manic episodes – compared to an age, gender and education matched sample of healthy control participants. A particular emphasis will be laid on the deficits and proportion of clinically impaired participants.

Methods: Patients with first episode mania (FM, n= 34) or previous untreated mania (PM, n= 21) were neuropsychologically tested after their first treated manic episode, along with 110 matched healthy control comparison subjects. The cognitive domains evaluated included verbal- and visual learning and memory, attention, processing speed, executive functioning and IQ. Results were corrected for speed of processing differences, and compared to clinical symptoms as well as previously reported results for multiepisode bipolar disorder patients.

Results: Patient groups showed impairments in psychomotor speed, attention, learning and memory, executive functioning and IQ. No significant differences in neurocognition were found between the two patient groups. When controlling for psychomotor speed, measures of visuoconstructive reasoning and motor dexterity remained statistical significance. The mean proportion of patients with clinically significant impairment was 18% for FM and 16% for PM. There were no significant relation between clinical symptoms and neurocognition, but indications of smaller deficits compared to multiepisode patients.

Conclusion: Neurocognitive dysfunctions are present early in the course of bipolar disorder and reaches the level of clinical significance for a subgroup of individuals. Comparing the results to neurocognitive findings in a non-overlapping sample of multiple-episode BD patients from the TOP study group, our findings also suggest that the neurocognitive dysfunction may increase with illness progression.

Paper III: Social functioning in first contact mania – clinical and neurocognitive correlates

Background: Social dysfunction occurs in more than half of all patients with bipolar disorder and is likely to be present early in the illness course. In the current report from the Thematic Organized Psychosis (TOP) study we aimed study the association between social functioning and neurocognition in a sample of first-episode bipolar disorder patients using both self- and clinician-rated instruments.

Methods: Patients with a first manic episode (FM, n= 34) or previous manic episodes (PM, n= 21) and 110 healthy control subjects (same sample as in paper II) matched for age, sex and education completed a self-report assessment form of social functioning, the Social Functioning Scale (SFS). Patients' level of functioning was rated by a clinician using the split Global Assessment of Functioning – Function scale (GAF-F), and the patients also underwent neuropsychological testing.

Results: Both patient groups had significantly lower self-rated social functioning compared to healthy controls on all subscales and total score of the SFS. Patients with previous untreated manic episodes tended to rate their functioning as more impaired than patients with a first manic episode. In multivariate analysis exploring the relationship to clinical symptoms and neurocognition, current depressive symptoms and processing speed had an independent contribution to self-rated social functioning, and psychotic symptoms to clinician-rated social functioning.

Conclusion: Impairment of social functioning in bipolar disorder is present already after a first manic episode, and is associated with a number of clinical variables although depressive symptoms had the strongest influence on self-rated social functioning. Neurocognition, except from processing speed, did not appear to have a significant influence on social functioning at this stage of the illness. Patterns of association were different for self-rated compared to clinician-rated functioning.

5. DISCUSSION

The main findings from the three papers in this thesis are discussed in light of previous and later research (5.1), implications of the findings (5.2), clinical implications (5.3) and methodological issues (5.4). Finally, the study's main strengths and limitations are raised along with suggestions for further research (6).

5.1. Main findings

5.1.1. Validation of the Norwegian version of the Social Functioning Scale (SFS)

Because we were interested in studying social functioning in first-episode BD, there was a need to investigate the reliability and validity of the instrument we had chosen for the measurement of social functioning. We examined the psychometric properties of the scale in a Norwegian sample, and since the scale had originally been developed for schizophrenia (SZ) patients only, we investigated its usefulness for BD participants also.

The main finding of this first paper was that SFS showed good psychometric properties also in its Norwegian version. The Chronbach's alphas were calculated based on the total sample (n= 300), and ranged from 0.60 to 0.88 for the seven subscales, with a score of 0.81 for the full scale. This is comparable to the original sample (SFS total score: 0.80 [subscales range 0.69 – 0.87]; Birchwood et al., 1990), and the translated Spanish version (SFS total score: 0.80 [subscales range 0.69 – 0.80] Torres & Olivares, 2005), indicating that the SFS can be used reliably in a broad range of clinical and language settings.

The seven subscales were found to form a single construct in accordance with previous reports, explaining 59% of the variance in the total sample. The component analysis supports the validity of calculating a single score as a measure of social functioning based on SFS ratings (Birchwood et al., 1990; Torres & Olivares, 2005). The one-component structure was maintained also for patients with BD. However, a two-component structure was suggested for the SZ group, with employment as a second dimension in addition to the other subscales.

For healthy controls, a three-component structure was suggested. A study including SZ patients and healthy controls, also reported a three-component structure of the seven SFS subscales (Pijnenborg et al., 2009). Total explained variance in their study was 70%. However, it was not clear if their analysis was performed on the total sample or was restricted to the schizophrenia group. Our findings are similar but not identical for both our SZ and healthy control groups, whereas our main analysis for the whole sample supports the validity of a single-component structure.

The SFS was found to be a valid measure of social functioning by its significant correlations of the SFS Total score with the GAF-F score in both clinical groups, with medium to large size effects (SZ: $r = 0.27$, $p < 0.05$; BD: $r = 0.46$, $p < 0.01$). Although the sub scales measure specific and limited functions, thus making them less suitable for a comparison with a global measure like the GAF, we correlated all SFS sub scales (scaled scores) for both diagnostic groups with the GAF-F (data not in paper). For the SZ group, the GAF-F correlated significantly only with two sub scales (Withdrawal and Interpersonal behaviour), whereas the GAF-F correlated significantly with all sub scales except Independence – competence in the BD group. Correlations were also higher in the BD group than in the SZ group. This suggests that the patients' self-report of social functioning share a moderate degree of the variance with the observed, clinician-rated functioning, and also that the SFS Total score can be used independently, especially for SZ patients.

The SFS did not correlate with age, sex and IQ in either diagnostic group, and can thus be used without correcting for these demographic variables. Regarding clinical symptoms, when correlating the SFS to other measures, we found moderate but significant correlations for negative symptoms, depressive symptoms, GAF-S, work ability and education. On the other hand, the GAF-F correlated moderately but significantly also to a number of clinical characteristics such as depressive symptoms, work ability, educational level, social situation and housing. This may be seen as an indicator that the two scales measure somewhat different aspects of social functioning. Overall, the SFS appears to measure more diverse, subtle and specific aspects of social behaviors that are also more independent of clinical symptoms.

Case-wise, the instrument was shown to reliably classify participants above chance level into their true groups, with a particularly good discrimination between healthy controls and patients – 94% of healthy controls were correctly classified. The best classification was found for people with SZ and healthy controls; one third of BD patients rated themselves similar to the profile of the SZ group. Therefore, in the current study SFS did not distinguish precisely between BD and SZ participants.

To investigate how sensitive the SFS total score was in assessing level of social functioning, we tabulated the distribution of scores for each group, using the same score ranges as in the original study (Birchwood et al., 1990). The HC scores clustered around a higher median than both SZ and BD participants. None of the individuals with SZ obtained scores within the highest range (126-135), compared to 9% in the BD group and 45% in the HC group. Scores below 115 were given to 82% of BD patients and 93% of SZ patients, while only 4% of the HCs rated themselves within this range.

There were significant group differences between the SZ, BD and healthy control groups for all subscales and total score. On subscales 5 – independence-competence and 6 – independence-performance the two clinical groups did not differ significantly. On all other subscale scores and SFS total score, the BD group scored better than the SZ but poorer than healthy controls. This was in the expected direction and suggests that patients with BD experience social dysfunction as reported in recent studies (MacQueen et al., 2001; Sanchez-Moreno et al., 2009).

In conclusion, the study has provided support for the reliability and validity of the Norwegian version of the Social Functioning Scale. The scale can be used on patients groups with both SZ and BD, and discriminates well between patients and healthy controls. The scale appears to measure slightly different aspects of of social functioning compared to the GAF-F, and to be less influenced by the effect of clinical symptoms.

5.1.2. Neurocognitive functioning in first contact mania

The main finding of this second paper is that neurocognitive deficits are present among BD patients already at the time of their first treatment for a manic episode. This applies to both the patient group with no previous manic episodes and to the patient group with previous untreated episodes. Despite differences in age at onset, number of episodes and treatment delay between the two patient groups, they were generally performing similarly on most neurocognitive measures. There were statistically significant differences between the patient groups and the healthy control group on measures of verbal recall, psychomotor speed, attention and some aspects of executive function as well as visuoconstructive reasoning. These results support findings from previous studies of neurocognition in first-episode mania with more limited samples (Nehra et al., 2006; Torres et al., 2010). The domain with the most prominent and statistically significant differences between groups was psychomotor speed. Here all measures except word reading was significantly lower in both patient groups compared to the HC group. Impairments in processing speed in BD is previously documented in the literature (Robinson et al., 2006) and has also been observed in unaffected family members (Ferrier et al., 2004; McIntosh et al., 2005), suggesting a heritable component. The domains with the least significant differences between groups were verbal learning and memory, executive functioning and IQ.

The groups were matched on age, gender and education, but not current or premorbid IQ. Of particular interest is the finding that premorbid IQ (NART) was found no different in the BD group compared to the HC group. We have previously reported the same pattern in BD groups with multiple episodes (Simonsen et al., 2008).

The degree of cognitive impairment varied across domains. An average of 18% of the FM group, 16% of the PM group and 7% of the HC group were considered clinically impaired across cognitive measures. On the learning and memory tasks, 23% of FM and 14% of PM compared to 7% of the HCs had clinically significant impairment. Impairment of psychomotor speed was found in 21% of FM and 25% of PM participants compared to 7% of HC participants. For attention and working memory, and average of 13% of FM and 12% of PM participants were considered clinically significantly impaired, whereas 4% of HC participants had impairment on these tasks. Regarding executive functioning, 15% of FM,

11% of PM and 6% of HC participants had clinically significantly cognitive impairment. On the IQ measures, 17% and 19% of the FM and PM groups had impairment, compared to 8% of HC participants. Overall, twice as many participants from the two bipolar disorder groups had clinically significant cognitive impairment compared to healthy controls.

Comparing the present findings to the results from our group's previously published study of BD patients with multiple episodes (Simonsen et al., 2008), we found that the magnitude of dysfunction in first contact mania patients was comparable to multiple-episode BD patients on certain measures of verbal recall (CVLT-II delayed recall) and executive functioning (Color-Word Interference test). For the remaining tasks which includes verbal learning (Logical Memory and CVLT-II learning), attention (Digit Span backwards, Bergen n-back) and other measures of executive functioning (Verbal fluency), consistently smaller cognitive deficits were present in first contact mania patients compared to multiple-episode BD patients. The consequences of this finding will be further discussed under (5.2.) Implications.

Contrary to expectations there was a lack of associations between clinical variables such as number of manic episodes and neurocognition. We did find a trend towards a significant association between level of depression and a measure of executive functioning (verbal fluency set shifts), in a direction indicating that higher levels of depression was associated with a better performance. This is in contrast to most previous findings. For instance, increased severity of depressive symptoms in unipolar major depression has been shown to be significantly associated with reduced cognitive performance across episodic memory, executive functioning and processing speed (McDermott & Ebmeier, 2009). In BD, depressive symptoms have also been associated with dysfunctions in psychomotor speed, speed of information processing and attentional switching (van der Werf-Elderling et al., 2010).

When correcting for psychomotor speed (Digit Symbol Coding), two neurocognitive measures (Grooved Pegboard and Block Design) remained statistically significant, and a third measure (Letter-Number Sequencing) lost its significance after Bonferroni correction. This

might suggest that motor speed, attentional and visuoconstructive measures are the most sensitive tests in this sample.

In conclusion, we here show that neurocognitive dysfunction is present early in the course of BD and reaches the level of clinical significance in a subgroup of individuals. Comparing our results with multiple-episode patients, the findings also suggest that the neurocognitive dysfunction may increase with illness progression.

5.1.3. Social functioning in first contact mania

The main finding of this last paper was that the BD patients displayed evident signs of social dysfunction after their first treatment for a manic episode. Both the FM and PM groups scored significantly lower on all subscales of the SFS compared to healthy controls. This included interpersonal relationships, leisure activities, skills necessary for independent living, and work functioning. These findings are consistent with findings from studies of more chronic BD patients (Haro et al., 2010; MacQueen et al., 2001) as well as studies of patients early in the illness course (Kauer-Sant'Anna et al., 2009; Torres et al., 2010). Patients with previous manic episodes rated themselves lower than patients with a first manic episode on the subscales Independence-Competence, Prosocial activities and Employment – as well as having a significantly lower SFS Total score.

There was no association between premorbid social functioning and current social functioning. The findings from our sample also show a normal functioning up until illness onset in both clinical groups. Cannon et al (1997) reported contrary to our results that adult-onset BD had significantly poorer overall and adolescent premorbid adjustment than healthy controls and that the BD group did not differ from a schizophrenia comparison group on sociability. However a later study could not confirm this finding (Uzelac et al., 2006).

When correlating the measures of self- and clinician-rated social functioning with clinical measures, we found a significant relationship between a number of clinical variables and social functioning. Regarding self-rated social functioning (SFS), cannabis use was

significantly negatively correlated with social functioning, indicating that patients who reported having used cannabis also reported poorer social functioning. Current depression and number of depressive episodes was also significantly negatively correlated with self-rated social functioning, showing that the more depressive symptoms or episodes the worse social functioning. There was also a positive correlation between age at onset and SFS indicating that a better functioning was associated with a later onset of BD. The relationship between earlier age at onset and reduced social functioning has been reported in previous studies (Meeks, 1999; Perlis et al., 2009).

Regarding the GAF-F, clinician-rated social functioning was correlated with psychotic-, depressive- and manic symptoms showing that a higher symptom load was associated with poorer clinician-rated functioning.

The relationship between depressive- or subclinical depressive symptoms and impairment of social functioning have been reported in several investigations (Bonnin et al., 2010; Fagiolini et al., 2005; Kauer-Sant'Anna et al., 2009; Martino et al., 2009; Mur et al., 2009; Simon et al., 2007). Manic and psychotic symptoms were associated with lower clinician-rated social functioning but not lower self-rated social functioning. Morriss et al (2007) reported that hypomanic symptoms increased friction and impaired adjustment with the extended family, and Judd et al (2005) reported a stepwise progression in disability associated with each increment in manic or hypomanic symptom severity in BD I. Although we did not investigate use of other illegal substances than cannabis, previous studies have reported that substance use disorders (Mazza et al., 2009; Weiss et al., 2005) or excessive substance use including cannabis (Lagerberg et al., 2010b) are associated with poorer social functioning.

There were no significant correlations between neurocognition and self- or clinician-rated social functioning. This is in contrast to other findings (Altshuler et al., 2008; Bonnin et al., 2010; Martinez-Aran et al., 2007; Martino et al., 2009; Mur et al., 2009), including a study on non-first episode BD from our own TOP study group, that reported both self-rated (SFS Total score) and clinician-rated (GAF-F) social functioning correlating significantly with five neuropsychological measures and symptom ratings (Simonsen et al., 2010). However findings from another study of a first-episode BD group are in line with our results. Here

Torres (Torres et al., 2010) reported an association between baseline neurocognition and 6-month functional outcome, however they failed to find an association between baseline cognition and concurrent baseline psychosocial functioning in newly diagnosed BD patients.

Results from the multiple regression analysis show that both depressive symptoms and surprisingly, good processing speed, had an independent contribution to self-rated social functioning. The latter is rather contrary to expectations, but it is possible that individuals with a better cognitive functioning are more aware of their social difficulties, or have a higher standard of what they think they should be able to manage. Only psychotic symptoms significantly influenced clinician-rated social functioning.

In conclusion, impairment of social functioning in BD is present already after a first manic episode. Patients with more previous mood episodes and longer treatment delay reported more social impairment and were less likely to be engaged in full-time employment or studies. The main predictors for both self-rated and clinician-rated social functioning are clinical symptoms, with depression associated with self-rated function and psychotic symptoms with clinician-rated function. Processing speed had a significant influence on social functioning, while other neurocognitive measures did not appear to play a significant role in social functioning at this stage of the disorder.

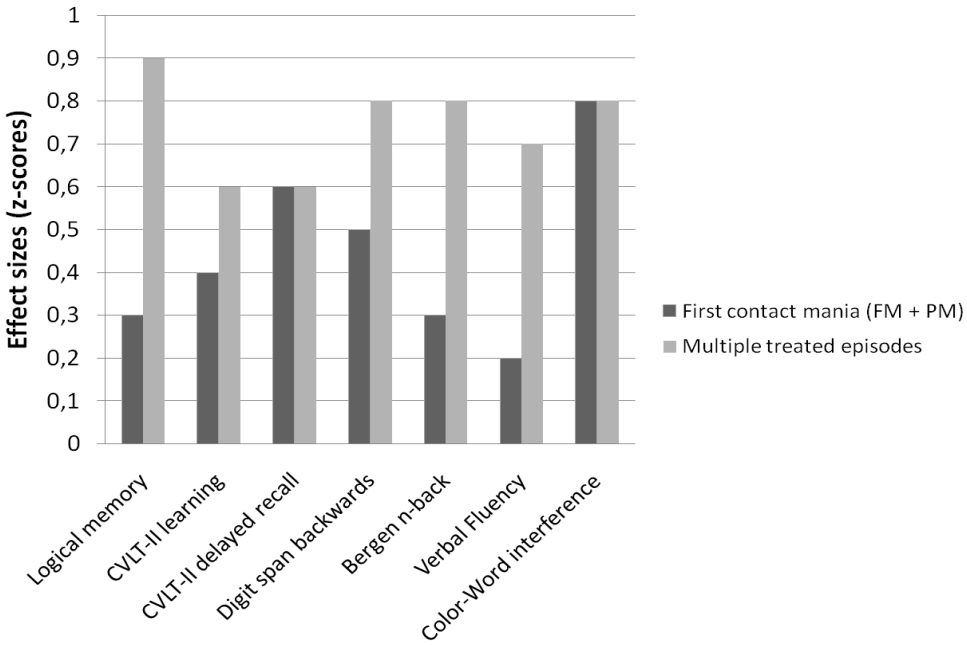
5.2. Implications

5.2.1. Evidence for accelerated cognitive decline?

As previously mentioned, there were clear signs of neurocognitive deficits in patients with BD already after treatment of a first manic episode. Psychomotor speed was the most impaired cognitive domain in both BD groups compared to the HC group, but the patients also had significant impairment on measures of attention, verbal recall, executive functioning and visuoconstructive reasoning, consistent with findings from previous meta-studies of neurocognitive impairment in BD (Bora et al., 2009; Kurtz & Gerraty, 2009;

Robinson et al., 2006; Torres et al., 2007). Comparing the results to a non-overlapping sample of multiple-episode BD patients (Simonsen et al., 2008) provides a preliminary framework for determination of the longitudinal course of cognitive impairment of the illness.

Figure 1: Patient-control performance in First contact mania (FM and PM groups combined) and Multiple treated episodes BD



The figure shows that the magnitude of dysfunction in the total first contact mania sample is comparable to the multiple-episode sample on verbal recall and some aspects of executive functioning. For the remaining tasks, consistently smaller deficits are present in the first-episode BD group. This might suggest that cognitive impairment in certain domains may

progress with advancing illness course, while others may already be impaired at illness onset. However as this is a comparison of cross-sectional data, it is possible that the differences in magnitude of cognitive impairment are related to characteristics of the samples, particularly the multiple-episode group. For instance, the persons in the multiple-episode sample might represent a subgroup with a more adverse illness course and more cognitive dysfunction, which makes them remain in the specialized health-care system over several years.

Torres and colleagues (2010) compared findings from their sample of first-episode BD patients to previously published meta-analytic data of multiple-episode patients and found comparable cognitive deficits on tasks of premorbid/verbal intellectual ability and attention/processing speed, while deficits in executive functioning and verbal memory were consistently smaller in the first-episode patients. Although the findings differed somewhat from our results, they too suggest that cognitive impairment in certain domains may progress somewhat over the course of BD.

Cognitive functioning have been negatively related to number of episodes, number of hospital admissions and duration of illness (Robinson & Ferrier, 2006), but this could also be interpreted as patients with greater cognitive impairment being less able to manage their illness with a poorer illness course as a result. A 2-year longitudinal study of euthymic BD outpatients showed that impairment in executive function and processing speed was maintained over the time period, and these deficits seemed to be persistent but stable over time (Mur et al., 2008). However, the patient sample had an average duration of illness of 17 years at entry of the study, which might explain why no decline in any cognitive functions during that period was found. Alternatively, cognitive impairment may manifest in early life, but significant decline may not be apparent until late middle or older age. Gildengers et al. (2009) investigated longitudinal cognitive functioning in older persons with BD, and found that they presented with more cognitive dysfunction and more rapid cognitive decline than expected given their age and education. The evidence for an accelerated cognitive decline in BD is still preliminary and neurodegeneration may or may not be the correct term for the harmful effects of repeated episodes and neurotrophic medications on cognitive performance (Goodwin et al., 2008). More longitudinal studies, preferably on first-episode

patients are needed to explore the relationship between illness course and cognitive impairment.

5.2.2. Neurocognitive impairment independent of clinical course and social dysfunction?

Apart from a trend towards a significant association between level of depression and a measure of executive functioning, we did not find any significant relationship between neurocognitive impairment and clinical characteristics such as manic or psychotic symptoms, or the number of episodes. This is in contrast to previous research (el-Badri et al., 2001; Robinson & Ferrier, 2006), and it also questions the strong association between illness progression in the form of manic episodes and neurocognition suggested by previous studies (Lopez-Jaramillo, 2010). Some areas of neurocognitive functioning have been suggested as illness traits rather than state variables. For instance, sustained attention deficits has been demonstrated in euthymic BD patients, and there are preliminary indications that this deficit is present from the first episode, but also becomes more severe with the progression of the disorder (Clark & Goodwin, 2004). Impairments in verbal learning and memory have also been found to be persistent during the euthymic phase of BD and may represent trait variables, but are also related to the number of affective episodes (Cavanagh et al., 2002). Impulsivity in BD has also been suggested having both affective state-dependent and trait components (Strakowski et al., 2010). This profile of trait impairment combined with state modulation is interesting because it provides a link between etiological factors and the processes that trigger and exacerbate symptoms during acute episodes. Our neurocognitive results thus seem to be independent of the clinical course at this specific stage of the illness, and might therefore represent trait variables. Alternatively, the lack of findings might be based on lack of statistical strength, since the design of the study necessary set restrictions on the number of previous mood episodes, especially elevated mood episodes.

Contrary to previous findings (Wingo et al., 2009) there was no significant correlations between neurocognitive functioning and self- or clinician-rated social functioning. However, the findings are in line with an equivalent study of first-episode BD patients that also failed to find an association between baseline neurocognition and social functioning (Torres et al.,

2011). It is possible that baseline ratings may have overestimated disability or the relatively high level of depressive symptoms might have disturbed the relationship thus compromising the power to detect expected associations. The multiple regression analysis revealed a significant relationship between Digit Symbol, a measure of processing speed, and self-rated social functioning. Processing speed have been related to impaired social functioning in other studies (Mur et al., 2008; Tabares-Seisdedos et al., 2008), and one study of BD patients followed up 15 years after an index manic episode found that Digit Symbol was the sole predictor of social functioning in that sample (Burdick et al., 2010). However, the direction of both non-significant correlations and multiple regression in our findings were rather unexpected, suggesting that patients with a good cognitive functioning rated themselves as having a poorer social functioning. A possible explanation might be that individuals with a better cognitive functioning are more aware of their difficulties related to for instance relationships, work and self-care, or they might be more likely to compare themselves to peers or have a higher expectation of what they think they should be able to manage. Bowie and colleagues (2007) have also reported better cognitive skills among schizophrenia patients who underestimated their everyday real-world performance. Similarly, individuals with poor cognitive functioning might be less aware of their social difficulties, which could be related to insight. In a report from the TOP study group, Engh and colleagues (2011) demonstrated that overconfidence in own beliefs was associated with cognitive dysfunction in schizophrenia. Working memory deficits have also been related to poorer general insight in bipolar disorder (Varga et al., 2007).

5.2.3. Premorbid and current social functioning in first contact mania

Both the FM and PM groups' premorbid self-reported social functioning was good up until illness onset. Not many studies have investigated this previous to the current study, and results have been conflicting (Cannon et al., 1997; Uzelac et al., 2006). The finding that premorbid functioning was not impaired in the first contact mania patients is in contrast to findings from studies of patients with schizophrenia (Norman et al., 2005; Saracco-Alvarez et al., 2009.) Findings from first-episode psychosis patients has found impairment in premorbid functioning (Monte et al., 2008) and even young people at clinical high risk for psychosis

have demonstrated significant deficits in social functioning at the pre-psychotic phase of the illness (Addington et al., 2008). Accordingly, the findings from our study suggest that impairment in social functioning is related to the onset of BD.

Regarding current social functioning, both FM and PM group members rated themselves as lower functioning on all SFS subscales compared to the HC group. They were also evaluated as moderately impaired by the research fellow. These findings show that patients with BD have substantial functional impairment early in the course of the illness. A number of clinical characteristics were related to level of functioning among the patients with first-episode mania. Depressive symptoms correlated significantly with both self- and clinician rated social functioning. Cannabis use, age at onset and number of depressive episodes was significantly associated with self-rated social functioning, while current positive psychotic- and manic symptoms was significantly related to clinician-rated social functioning. Taken together, the findings from premorbid- and current social functioning suggests that impairments in functioning are related mainly to illness onset and the clinical symptoms associated with having BD. This differentiates BD from schizophrenia regarding functioning, as premorbid functional impairment is believed to be present before illness onset in schizophrenia.

5.3. Clinical implications

5.3.1. The impact of cognitive impairment

About 1/6 of the first contact mania cohort had clinically significant neurocognitive impairment – meaning that impairment would be so severe that it would be expected to interfere with everyday life. Results from multiple-episode BD patients from the same catchment area showed that 1/4 of the group had clinically significant cognitive impairment (Simonsen et al., 2009).

The clinical impression of patients with BD as a group is often a relatively heterogeneous one. Many patients seems to have satisfactory functioning between episodes, a more benign course of illness and little psychiatric comorbidity, while others have a worse illness course and poorer functioning between episodes. The same could perhaps be the case for cognitive functioning, as a subgroup of patients with BD experience clinically significant cognitive impairment that is likely to interfere with their functioning at work, school or other activities of daily life. However, the majority of BD patients *do not* have clinically significant cognitive impairment. Still, cognitive impairment causes subjective distress among many patients with BD, and is related to poor treatment adherence in BD patients, although the causal relationship is uncertain (Martinez-Aran et al., 2009). Regarding possible interventions specifically targeting cognitive dysfunction, cognitive remediation have traditionally received much more investigation in the schizophrenia field, but later research shows promising results for patients with BD as well (Deckersbach et al., 2010). These findings underline the importance of assessing neurocognitive functioning in patients with BD, and suggest that at least a subgroup of patients are in need of treatment aimed at enhancing cognitive functioning.

5.3.2. Group differences between patients with a first manic episode and patients with previously untreated manic episodes

The FM and PM groups differed on a number of important clinical characteristics. The PM group had a longer treatment delay, an earlier age at onset, and more previous mood episodes of both polarities as well as more psychotic episodes. Accordingly, the group differences found in social functioning may not necessarily relate to the number of manic episodes per se. Patients in the PM group tended to rate themselves as less competent in performing skills necessary for independent living and participated less in social activities than FM group members. They were also less likely to be engaged in full-time employment, due to being on a medical leave, which possibly is a consequence of a more severe illness course.

Number of previous episodes (MacQueen et al., 2000) and an earlier age at onset of BD (Perlis et al., 2009) has previously been associated with a poorer functioning in BD. We did in fact find that lower self-rated social functioning was significantly correlated with both earlier age at onset and more depressive episodes. Interestingly, no differences in clinician-rated functioning were found between the groups. It could be that people who have suffered from the illness for a while, lose confidence in their own ability to function. Another possibility might be that being left out of a productive work setting also limits other areas of functioning – for instance having a smaller social network or not having financial means to participate in certain activities like visits to a restaurant or theater.

5.3.3. The impact of depressive symptoms on social functioning

Impaired social functioning was related to current depression and number of depressive episodes. On average both patient groups were mildly depressed. It has previously been found that BD I patients primarily have a depressive rather than manic symptomatic structure, and subsyndromal and minor affective symptoms predominate the illness course (Judd et al., 2002). The presence of residual symptoms at remission from depression appears to have long-term clinical significance. Longitudinal studies of patients with subclinical depression after a major depressive episode has found that they experience more depressive symptoms and minor depression over time (Judd et al., 2000; Kennedy et al., 2004) and showed greater impairment in longitudinal social adjustment (Kennedy et al., 2004). Depressive symptoms also play a major role in the quality of life (QoL) in patients with BD (Brissos et al., 2008). Even minor depressive symptoms have been associated with reduced QoL (Nierenberg et al., 2010). Full functional recovery after an episode of depression should therefore be the goal of treatment as enduring residual symptoms lead to long-term psychosocial impairment (Kennedy et al., 2007).

5.3.4. The use of the SFS as a self-rating scale for social functioning in BD

The findings of this thesis suggest that the Social Functioning Scale is a reliable and valid self-rating instrument for patients with BD. The scale is easy to administer and provides information of the individuals' functioning in a wide range of social and functional domains. It appears to measure more diverse, subtle and specific aspects of social behaviours than the GAF, and is possibly more independent of clinical symptoms. Difficulties related to social functioning is present already after a first treatment episode in BD, and functioning is perceived as impaired among both clinicians and patients. This implies that not only the management of clinical symptoms but also that therapeutic strategies are needed to improve the functional recovery of BD patients. The SFS could be a useful tool in assessing social functioning in several domains, and detect changes in functioning during the course of treatment.

5.4. Methodological issues

5.4.1. Study population, sample representativity

The clinical samples included in the current three papers as part of the TOP study population, were recruited consecutively from a naturalistic treatment setting. All patients were recruited from out- and inpatient units across the four largest psychiatric hospitals in Oslo and the surrounding area. The Norwegian mental health care system is based on catchment area based patient admittance, and offers public mental health care to all individuals with mental illness within the given area. The absence of private mental health care hospitals or units in Norway suggests that the study population is to a large extent representative for individuals with BD or schizophrenia receiving treatment from psychiatric units.

Patient inclusion was based on referrals from their treating clinicians, thus dependent on the clinicians' initial assessment of which patients would be suitable candidates for the study,

and their understanding and positive attitude towards the aim of including all eligible patients in the study. To ensure the inclusion of as many patients as possible, the TOP study clinical assessment team members had their base in one or two clinics where they attended regular staff meetings reminding clinical staff of the ongoing studies and discussing possible cases.

It is possible that participants with a positive attitude towards research or 'higher functioning' individuals with academic interest were more likely to take part in the study. This is supported by the fact that both the clinical and healthy control participants had a relatively high IQ compared to other studies in the field, but it could also suggest that outpatients and non-acute inpatients are better functioning than chronic hospital cohorts often used in other studies. The exclusion criteria for the study aimed at controlling the effect of medical problems, learning disabilities (IQ below 70) and poor Norwegian skills across clinical and control participants, as well as own or family history of psychiatric disorder or substance abuse in healthy controls. This will also have excluded those with poorest functioning. Due to the personal data filing system act, it is not possible to register characteristics of patients refusing to participate in research studies. We can only speculate in what the reasons for declining might be, like a poorer illness insight, more persecutory symptoms (especially for the schizophrenia patients) or not wishing to be associated with a mental illness. These factors are however common to all studies based on informed consent.

The term *first contact* mania was used to define the overall patient sample in paper 2 and 3. The definition is somewhat challenging. The participants were characterized as first contact mania if they met the diagnostic criteria for DSM-IV BD I disorder, and were or had been receiving their first adequate treatment for a manic or mixed episode no more than 12 months before inclusion. Because the patients might have had multiple depressive episodes or even unidentified and untreated manic episodes prior to inclusion, the clinical characteristics of the sample varied considerably. However, this is in line with the small amount of previous studies of first-episode BD, which also suggest that early BD patients are difficult to identify and engage in research studies compared to other first-episode psychotic disorders. Possible reasons for this could be that the persons with early symptoms of BD do

not seek specialized health care and are being treated by their general practitioner/family physician, or that initial depressive episodes are not recognized as BD. More restricted criteria for a first episode, for instance no previous episodes of elevated mood would also limit the sample, both regarding statistical power but also in respect to its generalizability to clinical samples.

To assure a representative clinical sample there was no a priori control of potential clinical confounders such as the presence of current symptoms, substance abuse and use of medication. Consequently, the degree of present symptoms varied from symptom-free to severe symptoms, especially depressive symptoms, duration of illness varied from having had one or a few episodes to multiple episodes, and the extent of substance abuse and medication use also varied. As a result, the findings in this thesis should be generalizable to a clinically heterogeneous sample of individuals with BD and SZ receiving treatment as usual in a mental health care setting.

5.4.2. Possible confounders

Because this is a naturalistic study, there is little control with potential confounding variables. There was also little a priori control by initial study design as we aimed to include as many persons with first contact mania as possible. However we tried carefully to identify potential confounders.

Gender, age, IQ and education are known to influence neurocognitive test results. Men have shown a better performance on some visuospatial tasks, while women perform better on some verbal tasks (Halpern, 1997; Kern et al., 2008). Age and education have been associated with lower cognitive performance with increasing age and lower education (Kern et al., 2008; Schaie, 1994). In paper 2 and 3 the first contact mania and healthy control groups were therefore matched for age, gender and education. Although not matched for IQ, the BD group did not differ from healthy controls on both premorbid IQ (NART) or full scale IQ (WASI). IQ below 70 was controlled for by the study design in all three studies.

Age (Tohen et al., 2000) and gender (Abel et al., 2010) have been shown to affect social functioning in severe mental illnesses. Gender differences have also been reported when using the SFS; with women reporting better functioning than men (Vaskinn et al., 2011). In the first paper, the three groups – SZ, BD and HC were not deliberately matched, however they did not differ in gender distribution, but the BD group was significantly older than the other two groups. The three groups also differed significantly from each other on IQ in the expected order; SZ < BD < HC. The SZ group had also significantly less education than the other groups. As schizophrenia patients have been shown to have a lower IQ in several studies (Urfer-Parnas et al. 2010) this could be related to illness specific features. The fact that the groups differed significantly in age and IQ in paper 1 could be a source of error. However, neither age nor IQ were significantly correlated with the SFS or the GAF-F, and only a modest significant correlation was found for sex and the GAF-F, suggesting they did not confound the main results.

There are a number of clinical variables that have been known to influence both neurocognition and social functioning in BD.

Clinical symptoms, such as manic or depressive states, have been shown to have a significant effect on neurocognitive performance in BD (Kurtz & Gerraty, 2009), as well as the number of episodes and duration of illness (Robinson and Ferrier, 2006). Several studies in the field have therefore used symptom free samples in order to control the effect of current symptoms on neurocognitive functioning (Bora et al., 2009; Torres et al., 2007). This is important in order to show that neurocognitive dysfunction is trait rather than state specific. However, the aim of paper 2 was to assess neurocognition in a naturalistic clinical setting and explore the possible relationship between symptoms and other early illness characteristics and neurocognitive functioning. It was therefore essential to include a sample with adequate variation. Depressive symptoms was the most frequent symptoms in this sample; nearly 60% of the total BD sample had depressive symptoms varying from mild to very severe symptoms, but little or no manic or psychotic symptoms. Although some trends towards significance was noticed, no significant correlations between early phase clinical

characteristics and neurocognition were found, suggesting that level of current symptoms did not explain the neurocognitive group differences between BD and HC participants.

Two recent reviews found a number of clinical factors associated with poor social functioning in BD, including depressive symptoms, psychotic features, early onset, number of hospitalizations, and anxiety (Huxley & Baldessarini, 2007; Sanchez-Moreno et al., 2009), suggesting that a more adverse clinical course may be related to social dysfunction. In paper 1, both SZ and BD sample were on average mildly depressed and in paper 3 as previously mentioned more than half of all participants had variyng degrees of depressive symptomatology. During depressive episodes, people with BD tend to display negative cognitive styles comparable to persons with unipolar depression, and this pattern has been demonstrated across measures of how people regard themselves, their life events, and their need to accomplish (Johnson and Tran, 2007). It is not unlikely that a negative cognitive style might have biased depressed individuals to rate themselves as poorer functioning than they actually are. Depressive symptoms are in addition associated with social withdrawal, decreased energy, low self-esteem etc. that also influence social behavior.

Substance abuse has been reported to both improve and reduce neurocognitive functioning (Balanza-Martinez et al., 2010; Ringen et al., 2009) and to reduce social functioning in BD (Huxley & Baldessarini, 2007; Lagerberg et al., 2010). We did, however, not exclude patients with any substance abuse, in order to assure a representative clinical sample. Regarding cannabis use, the most frequently used drug in the BD group, 55% of the total sample of BD participants reported having ever used cannabis during their lifetime. Only 4 patients in the FM group and 2 patients in the PM group had ongoing substance abuse or dependency (including alcohol). When removing these patients from the analyses in article 2, results remained unchanged and thus ongoing substance abuse was not found to have a significant impact on neurocognitive functioning.

Medication use may affect neurocognitive functioning in BD, and the risk for medication-associated cognitive side effects seems to increase with polypharmacy and the use of high doses (Balanza-Martinez et al., 2010). While antipsychotic medications have been related to significant cognitive deficits in most cognitive tasks (Torent et al., 2011), lithium has been

associated with lower impairment (Martinez-Aran et al., 2007). Nearly all of the patients in the present investigations were on medication compared to none of the healthy controls. Only 14% of the total BD sample in paper 2 and 3 were unmedicated, the remaining participants received different combinations of medications. A relatively large proportion of the total sample (73%) received antipsychotic medications. Regarding psychomotor speed deficits for instance, we cannot rule out the effects of medications on the performance. Although several studies have found that treatment with antipsychotic medication, especially chlorpromazine (Knowles et al., 2010) cause an impairment in psychomotor functioning, other studies have detected an improvement of psychomotor speed after both atypical and conventional antipsychotic treatment in schizophrenia (Morrens et al., 2006). We did in fact find a significant positive correlation between defined daily dose of antipsychotic medication and the Grooved Pegboard test ($p = 0.004$), suggesting a slower performance of the motor speed task with increased medication dose. The impact of lithium on impairment of psychomotor speed tasks have been reported in a review (Pachet et al., 2003). However, as only nine patients were on lithium at the time of assessment, it is unlikely that the impairment would be a result of lithium treatment only. The effects of medications are also likely to be related to illness severity, for instance use of antipsychotic medications naturally has a very high degree of association with history of psychosis.

5.4.3. Measurements

Only standardized measures that are widely accepted, that overlap with other studies in the field, and have been tested for good psychometric properties have been used in these studies. The SCID-I interview has been found to yield highly reliable diagnosis for most axis I and II disorders (Segal et al., 1994). The IDS-C has satisfactory psychometric properties (Rush et al., 1996) and appears applicable to both in- and outpatients with different affective disorders (Rush et al., 1986). The PANSS is the most widely used measure of symptom severity in schizophrenia, and have good psychometric properties (Santor et al., 2007). The YMRS have also good reliability, validity and sensitivity (Young et al., 1978) and is the most commonly used scale for assessing treatment response in mania (Poolsup et al., 1999).

There are several challenges related to the measuring of social functioning. The use of rating scales to measure social functioning indicates that subjective and qualitative data are being quantified by the participants or the clinician. The operationalization of social functioning is also difficult, as it involves multiple domains. An individual might show good functioning in one domain and impairment in others, and this will not be noticeable in rating scales such as the GAF, as functioning in several areas will be averaged into one simple score. Finally, the measurement of social functioning also involves more theoretical questions of what good social functioning really entails. The fact that we used both self-rating and clinician-rating scales was regarded an advantage, as the likelihood of patients symptoms affecting self-rating was of a concern. The GAF was therefore used as a 'gold standard' in addition to objective observable measures of social functioning (such as having a job) when conducting the validation study of the Social Functioning Scale. The GAF is widely used to assess psychological, social and occupational functioning. The inter-rater reliability of GAF ratings, performed by trained clinicians or in research settings, has been shown to be excellent (Hilsenroth et al., 2000; Vatnaland et al., 2007). The validity and reliability of the GAF-scale in clinical practice have only scarcely been studied in naturalistic samples, however one study found rather poor inter-rater reliability of the GAF as well as poor discriminant validity with disease severity in a large naturalistic sample of outpatients with major depressive disorder (Grootenboer et al., 2011). Both symptom and function scores of the split GAF (Pedersen et al., 2007) have been found highly consistent across raters and units. For research purposes and with trained raters, the GAF is thus a reliable instrument.

The purpose of paper 1 was to assess the reliability and validity of the Norwegian version of the Social Functioning Scale for patients with schizophrenia, bipolar disorder and healthy controls. Although the study concluded that the SFS was a valid and reliable tool for measuring social functioning in severe mental illnesses also in Norway, there are methodological issues that need to be addressed. The study found low inter-item correlations, which might be a limitation of the scale. However, as the alpha values were satisfactory for all scales, the implication of reduced inter-item correlation is uncertain. Self-evaluation has been shown to be particularly impaired in people with schizophrenia, and

those impairments could lead to inaccurate estimation of skill levels (Harvey et al., 2007). On the other hand, a comparison between self-report ratings and ratings from informants show that agreement is highest for observable aspects such as functioning, and lowest for psychological aspects (Becchi et al., 2004). The statistically significant differences between the schizophrenia group and the BD group on all sub scales of the SFS suggests a real difference in social functioning among the groups rather than a response bias, as all observable measures such as employment status and living situation also differed significantly between the patient groups, favoring BD patients.

The use of different neuropsychological tests in various studies might be a disadvantage for the studies of neurocognition in BD, making direct comparisons somewhat challenging. Although cognitive impairment is recognized as an important clinical feature of BD, there is no standard cognitive test battery that has been developed for BD research. The MATRICS (Measurement And Treatment Research to Improve Cognition in Schizophrenia; Nuechterlein et al., 2008) test battery increasingly used in schizophrenia research also have been judged suitable for patients with BD, even if other tasks including more complex verbal learning measures and tests of executive functioning should probably also be considered (Yatham et al., 2010). The neuropsychological tests used in this study are widely accepted and overlap with many previous studies in the field. However, the assignment of specific tests into different domains is to some extent controversial, as many tests call upon several functions. There are also a degree of overlap between domains, for instance memory and executive functioning have been reported to share 50-60% of variance (Duff et al., 2005). As psychological attributes such as cognitive abilities cannot be measures directly, we need to obtain a sample of behavior that can be quantified and represented in numerical scores. Concerns about the ecological validity of tests and predictions have been addressed by many researchers (Lezak, 2004). Cognitive performance in a structured setting with few distractions may not reflect cognitive functioning in everyday life, with the distractions that are usually present in more natural settings. Some cognitive functions are also difficult to reflect in a laboratory setting, such as the ability to initiate goal directed behavior (executive functioning). Lack of motivation or anxiety in the test situation may have a negative influence on test performance. As patients underwent quite extensive clinical and cognitive

examinations there was a concern that they would experience the involvement in the study as exhausting. We tried to address the problem with poor motivation by only include participants with a valid test performance assessed with a forced recognition task (Delis et al., 2004).

5.4.4. Ethical considerations

The TOP study is approved by the Regional Committee for Medical Research Ethics, and all participants gave their written informed consent before entering the study. Although the ethical sides of the project are officially approved, some aspects will be addressed. The patients in all three studies have severe mental illnesses with symptoms that might interfere with reality testing, making "informed consent" a possible challenge. Therefore, their psychiatric condition was thoroughly evaluated by their treating clinician in collaboration with the research fellow before asking the patient to participate. Patients were also told that they could leave the study at any time, with no questions asked, and that this would not have any consequences for their further treatment in the clinic. Both clinical and neuropsychological assessments are extensive, time consuming and probably tiring for the patients. The assessments were often broken down to several sessions on different days. Interviews were carried out at the patients' respective clinics or research offices, depending on what was most convenient for the patients. Patients were also offered taxi transportation to the research office if necessary. When assessments were completed, written reports from the neuropsychological testing and the clinical interview including a DSM-IV diagnosis were sent to the treating clinician with the patients consent. Patients were also offered an appointment with both interviewer and treating clinician present, where the information from the reports were presented and discussed. The general impression was that both the written reports and the feedback session were appreciated and considered useful by both clinicians and patients.

6. STRENGTHS, LIMITATIONS AND FUTURE RESEARCH

Strengths and limitations of the study have already been directly and indirectly discussed, but the main issues deserve to be highlighted. This is one of the first studies that have investigated the relationship between baseline neurocognitive functioning and baseline social functioning in first contact mania. To this date, only one previous study (Torres et al., 2011) has looked at this relationship in a first-episode BD sample. Recruitment through the Norwegian public mental health care system with a catchment area patient admittance system may have resulted in a relatively high degree of representativity compared to studies that have recruited from private clinics with more selected populations. Social functioning was examined using both clinician ratings and patients' self-report. This captures both patients' subjective experience in addition to an externally rated evaluation of their functional level. The instrument used to measure self-rated social functioning, the Social Functioning Scale, is validated on a Norwegian BD sample that is not overlapping with the first-episode patients. Rather than simply comparing the mean neurocognitive function for the clinical group to a sample of healthy controls, we investigated how many in each group had severe or 'clinically significant' cognitive impairment. This might give us an idea of how many patients who will actually experience difficulties in their daily life as a result of cognitive impairment.

One of the main limitations is that although the patients with BD were characterized as first contact mania because they had not received adequate treatment for a first manic episode before, many of them had had previous episodes with both elevated and depressed mood. We tried to attend to this by separating the patients into a first manic- and a previous untreated manic episodes group. Both the clinical and control samples have relatively high IQ compared to most previous findings, suggesting that we might have recruited fairly high functioning groups. Because the data is cross-sectional we cannot make inferences about causal relationships. The sample was not euthymic.

As this is one of the first studies to investigate the relationship between social functioning and neurocognition early in the course of BD, future studies should seek to replicate the findings from this particular study to support or disconfirm the findings in other first-episode mania samples. The fact that both our study and Torres and colleagues (2011) did not detect a significant relationship between neurocognitive functioning and social functioning in first-episode BD might be due to methodological issues, or it may be that this relationship is not detectable until the illness have progressed. A matched sample of multiple-episode BD patients would also be useful as a comparison group to look at difference in magnitude of neurocognitive dysfunction, and longitudinal studies of first-episode patients might be valuable to study illness progression. Future research should also investigate the use of cognitive remediation for persons with BD. Finally, the impact of a wider range of factors that might mediate the relationship between neurocognition, symptoms and social functioning should be explored, such as self-esteem, social cognition, personal attitudes and social support.

7. CONCLUSION

This thesis has investigated whether patients with BD recently treated for a first manic episode has neurocognitive deficits and social dysfunction, and to what extent these variables are related.

Firstly, the findings suggest that neurocognitive dysfunction is present early in the course of BD and reaches the level of clinical significance in a subgroup of individuals. Compared with multiple-episode patients the findings also suggest that cognitive impairment in certain domains may progress with advancing illness course, while others may already be impaired at illness onset.

Secondly, the findings suggest that impairment of social functioning in BD is present already after a first manic episode, and is associated with a number of clinical variables especially with depressive symptoms. Taken together, the findings from premorbid- and current social functioning suggests that impairments in functioning are related mainly to illness onset and the clinical symptoms associated with having BD. Thirdly, the findings did not support previous reports from non-first episode BD samples of neurocognition as a mediator for social functioning.

Finally, the findings underline the importance of assessing neurocognitive functioning in patients with BD, and suggest that at least a subgroup of patients are in need of treatment aimed at enhancing cognitive functioning. Additionally, complete functional recovery after an episode of depression should also be the goal of treatment as enduring residual symptoms most likely lead to long-term psychosocial impairment. Therapeutic strategies might also be needed to improve the functional recovery of BD patients. The SFS could be a useful tool in assessing social functioning in several domains, and detect changes in functioning during the course of treatment.

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I

II

Neurocognitive functioning in patients recently diagnosed with bipolar disorder.

Running head: Neurocognition in recently diagnosed BD

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Abstract

Objectives: Cognitive dysfunction in bipolar disorder (BD) is well established in the literature, however there are few studies of neurocognition in patients early in the course of the illness. In this study we compare neurocognitive function in a cohort of first contact mania patients with a healthy control group, matched for age, gender and education.

Methods: Patients with a first manic episode (FM, n= 34) or previous untreated manic episodes (PM, n= 21) were neuropsychologically tested following their first treated manic episode. A hundred and ten matched healthy control comparison subjects were also tested. The following cognitive domains were evaluated: verbal and visual learning and memory, attention, processing speed, executive functioning and IQ. Results were corrected for speed of processing differences, and were compared with previously reported results for multiple-episode bipolar disorder patients.

Results: BD patients early in their disease course showed impairments in psychomotor speed, attention, learning and memory, executive functioning and IQ. When controlling for speed of processing, measures of visuoconstructive reasoning and motor dexterity remained statistically significant. 18% of FM and 16% of PM patients were found to have clinically significant neurocognitive impairment. No significant relationship between clinical symptoms and neurocognition was found. The first contact mania patients studied were found to have smaller neurocognitive deficits compared to multiple-episode patients in previous studies.

Conclusion: Neurocognitive dysfunction is present in early bipolar disorder and is clinically significant for a proportion of patients. Our findings also suggest that neurocognitive dysfunction may increase with illness progression.

(246 words)

Keywords: bipolar disorder, first episode, mania, neurocognition, processing speed

Introduction

Cognitive dysfunction in bipolar disorder (BD) is well established in the literature. Meta-studies of neurocognition in multiple-episode BD patients have demonstrated deficits in standardized neuropsychological measures, including executive functioning, verbal learning and memory, attention and processing speed that persist during periods of euthymia (1-4). Results from previous studies from the TOP project show that BD patients have reduced performance in all measures of verbal memory , and in most measures of attention and executive functioning compared to healthy controls (5). However, the proportion of patients with BD who have clinically significant cognitive impairment varies between studies and is dependent upon the definition of neurocognitive impairment used, the measures of impairment employed and the proportion of BD subtypes (I and II) in the sample. Studies have reported clinically significant impairment ($\leq$ 1.5 SD below control group mean or scoring below the 5th percentile, respectively) in BD type I, varying from 3-36% (5) to 3.2-41.9% (6) , suggesting that more than half of people with BD do not experience cognitive difficulties. Several clinical factors may contribute to the variation in cognitive functioning, including a history of psychotic episodes (7), the number of previous mood episodes, the number of hospital admissions, illness duration (8; 9), age of onset of symptoms and duration of treatment delay (10; 11; 12). This indicates that cognitive dysfunction increases with illness progression, as suggested by a recent study, that included patients with long treatment histories, that showed an increase in cognitive dysfunction with an increase in number of manic episodes (13). However, it is possible that fewer episodes and good cognitive functioning over the course of the illness are expressions of a more benign form of BD rather than being causally related to each other. Evidence for progressive cognitive decline in BD is thus still inconclusive.

Neurodegenerative models have been used to explain neurocognitive deficits in at least some domains (14). Whether neurocognitive deficits reflect a global cognitive dysfunction or are a consequence of a primary deficit in core cognitive functioning remains unclear.

A meta-analysis has shown processing speed deficits to be present in patients with schizophrenia (15) and also in a twin sample of BD I patients (16). Deficits in processing speed in patients with schizophrenia have been shown to be associated with impairments in working memory and verbal learning (17). This adds to a growing body of work demonstrating the importance of processing speed to cognitive functioning and clinical outcome in severe mental disorders.

Most previous studies of neurocognition in BD have recruited patients with treated, multiple-episode BD. There are few studies with a cohort of patients early in the course of their disease. The recrutiment of a cohort with first-episode mania is difficult as first-episode mania is relatively rare in clinical practice. As it is not possible to give a diagnosis of BD type I until the patient has experienced their first manic episode, in most studies 'early in the course of the illness' denotes 'from the point of first treatment'. Two studies comparing patients with first episode BD with healthy controls found signs of executive dysfunction, but the sample sizes were small (18; 19). Studies comparing first-episode BD groups with other first-episode psychotic disorders, such as schizophrenia, have found either less severe cognitive dysfunction in BD (20; 21), or no clear group differences between the patient groups. There were differences in cognitive dysfuction in these groups compared to healthy controls (22; 23). A study comparing neurocognition in symptomatic first-episode BD patients with multiple-episode BD patients found no differences between the groups (18).A similar study surprisingly found poorer functioning in first-episode patients (24). However a bias may have present in this study as patient groups were not matched according to significant demographic and clinical variables. These studies also included small patient samples (N= 19 to 32), making the interpretation of findings and covariate analysis difficult. A recent study including a larger patient group (N= 45) (25) reported moderate effect size differences between euthymic BD participants who had recently experienced their first manic episode and healthy subjects. The measures employed assessed sustained attention, learning and memory, and nonverbal/spatial reasoning. The percentage of patients showing clinically significant cognitive impairment, i.e 1.5 SD below the mean of the control group, varied from 11-31% across tests. When comparing this data to previous meta-studies of multiple-episode euthymic BD samples (2; 3), the results indicate that the magnitude of cognitive impairment in first-episode BD was comparable to that found in multiple-episode BD for tasks that included premorbid/verbal intellectual ability and attention/processing speed. For tasks such as verbal memory and executive functioning there were consistently smaller cognitive deficits in first-episode patients (25). More studies on patients early in their disease course are necessary as this is a period where intervention may attenuate or prevent the changes that appear to emerge with chronicity (26).

The current study used a relatively large cohort of patients at first treatment for a manic episode (first contact mania patients). This cohort is comprised of two subgroups; one with no previous manic episodes (FM), and another consisting of patients who had one or more previous untreated manic episodes (PM).

The aims of the study was to investigate neurocognitive function in these two BD subgroups by comparing them to a healthy control group matched by age, gender and level of education, to examine the severity of the impairments, whether the impairments were clinically significant and whether patients were deficient in all domains or in just a number of domains. In addition, we investigated whether group differences can be explained by differences in processing speed. Another specific aim of the study was to examine if cognitive impairments are related to premorbid and early illness characteristics, in particular age at onset, duration of untreated illness and number of previous mood episodes (manic, depressive and psychotic).

Materials and methods

Participants

Participants with BD were recruited consecutively to the Early Bipolar Disorder Study, a section of the Thematically Organized Psychosis (TOP) Study group, from psychiatric inpatient and outpatient units at the major hospitals in the Oslo area, Norway. Patients were considered eligible for this particular study (i.e. first contact mania patients) if they met the diagnostic criteria for DSM-IV bipolar I disorder and were receiving their first *adequate treatment* for a manic episode. Since acutely manic patients are not always able to give informed consent, patients were included up to one year after the start of their first treatment. Patients were included if they had experienced previously untreated manic episodes, and if they had had a previous major depressive episode, whether treated or untreated. Fifty five patients in total met these inclusion criteria.

The cohort was divided into two subgroups. The Previous Manic episode subgroup (PM) consisted of patients who had had previous manic episodes that were neither identified nor adequately treated as such. The First Manic episode subgroup (FM) had only experienced the manic episode with which they presented. Healthy control (HC) participants were randomly selected from national statistical records from the same catchment area as the patients, and contacted by letter inviting them to participate. HC participants were excluded if they or any close relative had a lifetime history of a severe psychiatric disorder (schizophrenia, bipolar disorder and major depression), or if they had a history of substance abuse or dependency in the previous six months. For the purpose of this study

consecutive HC participants were matched in a ratio of 2:1 to patients on age, sex and education. The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. All patients received a complete description of the study before giving written, informed consent. The exclusion criteria for all groups were a history of hospitalization for head injury, neurological disorder, unstable or uncontrolled medical condition that interferes with brain function, IQ below 70 and age outside the range of 17-60 years. The participants also had to have Norwegian as their first language or have received their compulsory schooling in Norway, and to have scored 15 or above on the forced recognition trial in the California Verbal Learning Test (CVLT-II) (27).

Clinical assessment

Clinical assessment was carried out by trained psychiatrists and clinical psychologists. Diagnosis was based on the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) (28) and available medical records. Inter-rater reliability for diagnosis had an overall kappa-score of 0.77 (95% CI [0.60,0.94]) (29). Age at onset, polarity of first presenting episode and number of episodes were determined from the clinical interview and through examination of medical records. Polarity of first presenting episode was defined retrospectively as the polarity of the first SCID verified episode as indicated in the SCID protocol, and age at onset was the age at which the person had experienced this episode. Information about previous psychotic episodes (history of psychosis) was based on information from the SCID interview and medical records. The level of current symptomatology was defined based on the following scales: current depressive symptoms were rated using the Inventory of Depressive Symptoms-Clinician rated (IDS-C) (30), current manic symptoms were rated using the Young Mania Rating Scale (YMRS) (31), and current positive and negative symptoms were rated using the Positive And Negative Syndrome Scale (PANSS) (32). The effects of medication on cognitive performance on the day of testing was assessed using Defined Daily Dosages as the measure of the level of antipsychotic medication.

Neurocognitive assessment

Neurocognitive assessment was carried out by psychologists trained in standardized neuropsychological testing. A three-hour test battery was administered in a fixed order, including

two breaks. Measures included in this study have previously been found to be sensitive to dysfunction in schizophrenia and bipolar spectrum disorders (7).

Learning and memory was measured using three tests. The Logical Memory test (33), part of the Wechsler Memory Scale (WMS-III) (verbal learning and verbal recall); the California Verbal Learning Test (CVLT-II) (27), verbal learning and long delay free recall, and the Rey-Osterrieth Complex Figure Test (34), delayed recall.

Psychomotor speed was assessed with the following tests: Grooved Pegboard (35), measuring the average of left and right hand combined; Digit Symbol Coding, as contained in the Wechsler Adult Intelligence Scale (WAIS-III) (36), and the color naming task and the word reading task from the Color-Word Interference Test as contained in the Delis Kaplan Executive Functioning System (D-KEFS) (37).

Attention and working memory was assessed using the Digit Span and the Letter-Number sequencing from the Wechsler Adult Intelligence Scale (WAIS-III) (36) and the computer based Bergen *n*-back Test (N-back) (38) using d' as a measure of attention/working memory

Executive function was assessed using subtests of verbal fluency (letter fluency, category fluency and category switching) from the D-KEFS battery (37); the inhibition and inhibition/switching subtests from the Color-Word Interference Test contained in the D-KEFS (37) and the Wisconsin Card Sorting Test (39) measuring total errors, perseverative responses and number of correct categories achieved.

Premorbid IQ was measured using the National Adult Reading Test, Norwegian version (40)*, and IQ* was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI) (41) using the subtests Vocabulary, Similarities, Block Design and Matrix reasoning.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS for Windows, version 16.0, SPSS Inc., Chicago, IL, USA) was used for all statistical analysis. Between-subjects univariate analysis of variance (ANOVA) and chi-square analysis were used to compare group differences on demographic characteristics. The independent samples t-test or the Mann-Whitney U test were used to investigate group differences between the FM and PM groups with regard to clinical characteristics. Group differences in neuropsychological test performance was analysed using between-subjects univariate ANOVA with effect size (eta squared) of group differences and Scheffès post hoc tests. Bonferroni corrections were applied for all cognitive domains. Analysis of covariance (MANCOVA) was conducted by

entering Digit Symbol Coding as a covariate to investigate if, when psychomotor speed was controlled for, group differences in neurocognitive performance remained significant. In order to report effect sizes of the neurocognitive dysfunction, z-scores were constructed for each cognitive subscore based on the means and standard deviation of the control group, and a mean z-score for each domain was calculated. The proportion of participants with clinically significant cognitive impairment, defined as neurocognitive scores 1.5 SD below the average of the healthy control group was calculated, thus capturing participants performing below the normative seventh percentile level. Chi-square analysis was used to investigate group differences in clinical impairment. Non-parametric correlations (Spearman's rho) were used to assess the relationship between neurocognitive variables and clinical variables, with a level of significance determined at .01 due to multiple comparisons. Raw scores for all neurocognitive tests were reported.

Results

Demographic and clinical characteristics of HC and the FM and PM groups are presented in table 1 and 2 (TABLE 1+2 IN HERE). There were no group differences between the FM, PM and HC participants regarding age, education, gender or premorbid IQ (NART).

Clinical characteristics

The FM and PM groups did not differ significantly with regard to the polarity of their first episode, current clinical symptoms, or incidence of lifetime psychosis with 73% of the FM group versus 66% of the PM group having experienced psychotic symptoms. The number of patients with ongoing SCID-verified substance abuse or dependency did not differ significantly between the FM group (4 patients) and the PM group (2 patients). The groups differed significantly on age at onset of their first affective episode. The PM group was on average six years younger than the FM group at illness onset. The PM group also had significantly more depressive, manic and psychotic episodes compared to the FM group, and a significantly greater number of hospitalizations. There were also significant differences in treatment delay (time from first episode to start of adequate treatment), with an average of 1 year for the FM group and 8 years for the PM group. The groups did not differ

significantly regarding the type of medication they used, but significantly more patients in the PM group were unmedicated.

Neurocognitive performance.

The groups' mean performance for each neurocognitive measure and the respective analyses of variance with effect size estimates and Scheffès post-hoc tests are presented in table 3 (TABLE 3 IN HERE). Significant group differences were found in all cognitive domains with differences reaching the level of nominal significance in eleven of the single measures. Eight single measures remained statistically significant after Bonferroni-corrections.

The most statistically significant differences between the groups were with regard to psychomotor speed with all measures, except word reading completion time, lower in both the FM and PM groups compared with the HC group with medium to large effect sizes. Two of four measures of attention and working memory were significantly different in the clinical groups in comparison with healthy control group. There was a medium effect size difference between the FM group and the HC group on Digit Span backwards, and both clinical groups differed significantly, with medium effect sizes, from the HC group on the Letter-Number sequencing task.

The domains with the least significant differences between the groups were verbal learning and memory, executive functioning, IQ. The FM group had significantly lower scores than the HC group on CVLT-II recall, and both patient groups differed significantly from the HC group on the inhibition condition of the Color-Word interference test. A trend towards significance was also found for the Rey-Osterrieth Complex Figure Test and the inhibition-switching condition of the Color-Word interference test in both FM and PM groups in comparison with the HC group. Of the WASI subtests, only Block Design was statistically significantly lower in the two clinical groups, while a trend towards significance was found in the WASI subtest Matrix reasoning. Effect sizes for the statistically significant differences were small to medium.

After adjusting for psychomotor speed (Digit Symbol Coding), three of the eight statistically significant neurocognitive measures remained significant. These were Letter-Number sequencing, Grooved Pegboard and Block Design. Only the two latter measures remained statistically significant after Bonferroni corrections. Effect sizes were also reduced by 50% after Bonferroni corrections.

Clinically significant impairments

The proportion of FM, PM and HC participants with cognitive impairment within a clinically significant range for each subscore is shown in table 4 (TABLE 4 IN HERE). On average, 18% of the FM group and 16% of the PM group, compared with 7% of the HC group were considered clinically impaired across cognitive measures. With regard to learning and memory tasks, 23% of FM and 14% of PM compared to 7% of the HCs had clinically significant impairment. Impairment of psychomotor speed was found in 21% of FM and 25% of PM participants compared to 7% of HC participants. 13% of FM and 12% of PM participants were considered clinically significantly impaired in attention and working memory, whereas 4% of HC participants had impairment in these tasks. Regarding executive functioning, 15% of FM, 11% of PM and 6% of HC participants had clinically significantly cognitive impairment. On the IQ measures, 17% and 19% of the FM and PM groups had impairment compared to 8% of HC participants. Overall, twice as many participants from the two bipolar disorder groups as healthy controls groups had clinically significant cognitive impairment.

Group differences in neurocognition between the FM and PM groups

Neurocognition did not differ significantly between the FM and PM groups on most measures. However, the FM group was found to be significantly different from the HC group on CVLT-II recall and Digit Span backwards. The FM group was also significantly more impaired than the PM and HC groups on Logical Memory (learning condition), CVLT-II recall and Letter Number sequencing measures. The PM group was significantly more impaired than the FM and HC groups on Matrix Reasoning. The average proportion of clinically significant impaired patients was comparable in the FM and PM groups.

The relationship between early phase clinical characteristics and neurocognition in first contact mania

In order to investigate the influence of illness course and severity on neurocognitive performance, follow-up analysis was performed. The bivariate associations between clinical characteristics and neurocognitive functioning in the FM and PM groups combined are presented in table 5 (TABLE 5 IN HERE). There was a significant positive correlation between defined daily dose of antipsychotic medication and the Grooved Pegboard test (p= 0.004), suggesting a slower performance of the

motor speed task with increased medication dose. No other correlations between cognitive performance and clinical measures were deemed significant ($p<0.01$) although some trends ($p< 0.05$) towards significance were noticed. When investigating the potential influence of current symptoms we found a trend towards significance for the association between depressive symptoms, as measured by the IDS-C, and Verbal fluency set shift in a direction indicating that higher levels of depression were associated with a better performance. There was also a trend towards significance for depressive symptoms and Color-Word: color naming indicating that patients with more depressive symptoms needed a longer time to complete the task. Current elevated mood, duration of untreated illness and lifetime or current psychotic symptoms were not significantly related to any cognitive measures.

Discussion

The main finding of this study is that neurocognitive deficits are present in patients with BD at the time of their first treatment for a manic episode. This applies both to patients with no previous manic episodes and to patients with previous untreated episodes. We found statistically significant differences between the FM and PM groups and the HC group on measures of verbal recall, psychomotor speed, attention, visuoconstructive reasoning and some aspects of executive functioning. These results strengthen findings from previous studies with smaller sample sizes (24; 25). The groups were matched on age, gender and education, but not IQ. Of particular interest is that we did not find any differences in premorbid IQ (NART) between the BD groups and the HC group. Similar results have previously been reported in BD groups with a more chronic illness course (5). Despite differences in age at onset, number of episodes and treatment delay between the two BD patient groups they generally performed similarly on most neurocognitive measures and had the same level of clinically significant cognitive impairment. Levels of cognitive impairment in first contact mania patients appear to be less extensive than levels reported in more chronic- or multiple episode BD patients (1-6; 9), indicating that neurocognitive decline continues over the course of the disorder. Comparing the combined FM and PM groups to a non-overlapping sample of patients with

multiple treated episodes from the TOP research project (5) provides a preliminary framework for determination of the longitudinal course of cognitive impairment of the illness. (FIGURE 1 IN HERE).

Figure 1 shows that the magnitude of dysfunction in first contact mania patients is comparable to that in multiple treated episode BD patients on certain measures of verbal recall (CVLT-II delayed recall) and executive functioning (Color-Word Interference test; subtest 3 and 4 combined). For the remaining tasks, including verbal learning (Logical Memory and CVLT-II learning), attention (Digit Span, Bergen n-back) and other measures of executive functioning (Verbal fluency, 3 subtests combined), consistently smaller cognitive deficits are present in first contact BD patients than in multiple treated episode BD patients. The results of neuropsychological measures in a meta-analysis of 948 euthymic BD patients (42) were similar to those from the multiple treated patients (5). Both groups were slightly older than the first contact mania sample. The multiple treated episode patients were on average 38 years old and the sample from the meta-analysis was on average nearly 40 years old. This suggests that in certain domains, cognitive impairment progresses with advancing illness course, while other domains may already be impaired at illness onset. However, as some patients with BD are more in need of treatment and remain within the healthcare system, a selection bias may be present in these studies with an over representation of patients with severe BD. Longitudinal studies are necessary to fully investigate the development of neurocognitive dysfunction over the course of the illness.

Contrary to expectations, there was a lack of associations between illness history variables, such as number of manic episodes or duration of untreated illness, and neurocognitive functioning. This might be due to a lack of statistical strength as the design of the study necessarily set more restrictions on the number of previous elevated mood episodes than previous studies on multiple-episode patients. We found a trend towards a significant association between level of depression and one measure of executive functioning that is in line with previous findings. Increased severity of depressive symptoms in unipolar major depression has been shown to be significantly associated with reduced cognitive performance across episodic memory, executive functioning and processing speed (43). In BD, depressive symptoms has been associated with dysfunctions in psychomotor speed, speed of information processing and attentional switching (44). The findings of reduced verbal memory in healthy relatives of individuals with BD, indicating a genetic vulnerability to BD, (45; 46) suggest that some cognitive deficits might predate illness onset. Verbal learning and memory, especially long delayed recall, and verbal working memory are the most suitable cognitive endophenotypes to be used in genetic studies of BD (47).

The largest difference between patients with first episode BD and HC participants was in the area of psychomotor speed. This has previously been documented in the literature (2) and has also been observed in healthy family members (48;49) suggesting a heritable component to BD. When correcting for psychomotor speed (Digit symbol) only two neurocognitive measures, Grooved Pegboard and Block design, remained statistically significant. A third measure, Letter-Number sequencing, lost significance after Bonferroni correction. This suggests that motor speed, attentional and visuoconstructive measures are the most sensitive tests in this sample. Many higher cognitive operations involve internal dynamics that are speed-dependent. The kind of slowed information processing measuresd by Digit Symbol has been suggested as a central feature of the cognitive impairment seen in schizophrenia (15). Our findings are in line with a recently published paper by Antila and colleagues (50) who found that processing speed had a significant effect on nearly all other assessed cognitive functions among patients with BD I.

This study has several strengths and limitations. The main strength is the large and extensively characterized sample of patients who were early in the course of their treated illness. An associated weakness of the study was that as patients were assessed as close to the resolution of their first treated manic episode as possible, some were not truly euthymic but were deemed to be mildly depressed as per the average score on IDS-C. Cognitive performance can potentially be influenced by current symptomatology. However there were few, and in some cases contradictory, non-significant associations between depressive symptoms and neurocognitive functioning, suggesting a minimal influence of depressive symptoms on results. The age at onset and illness history measures were necessarily based on patients' retrospective memory and may have been influenced by recall bias. Medication effects can potentially influence cognitive performance. We found a significant association between defined daily dose of antipsychotic medication and motor speed but no association for other, more cognitively demanding tasks.

In conclusion, this study shows that neurocognitive dysfunction is present early in the course of BD and reaches the level of clinical significance in a subgroup of individuals. Comparing our results with those of studies of multiple-episode patients, the findings suggest that the neurocognitive dysfunction may increase with illness progression.

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Table 1: Demographic characteristics of the FM, PM and HC groups

	First episode mania (FM) N= 34	Previous untreated mania (PM) N= 21	Healthy controls N= 110	Group comparisons
Age, mean (SD)	31.2 (9.6)	30.5 (10.6)	31.1 (9.8)	$F_{(2,162)} = 0.4$, p= 0.961
Sex, m/f (% males)	15/19 (44%)	8/13 (38%)	49/61 (45%)	$\chi^2_{(2, n= 165)} = 0.3$, p= 0.860
Years of education, mean (SD)	13.1 (2.2)	12.9 (2.3)	13.4 (1.9)	$F_{(2,162)} = 0.5$, p= 0.592
Premorbid (NART) IQ, mean (SD)*	110.9 (6.6)	109.5 (5.1)	111.6 (4.9)	$F_{(2,160)} = 1.3$, p= 0.259

NART: National Adult Reading Test

* FM: 1 missing; PM: 1 missing

Table 2: Clinical characteristics of the first contact mania groups.

	First episode mania (FM) N= 34	Previous untreated mania (PM) N= 21	Group comparisons
PANSS Positive scale, mean score (SD) [Range]	11.6 (5.5) [7-27]	11.5 (3.8) [7-21]	n/s
PANSS Negative scale, mean score (SD) [Range]	9.6 (3.0) [7-20]	9.7 (3.8) [7-15]	n/s
Inventory of Depressive Symptoms – Clinician rated [1]			
Median score (min-max)	14 (0-39)	13 (0-50)	n/s
Young Mania Rating Scale, median score (min-max)	2 (0-28)	5 (0-19)	n/s
Age at first affective episode, any polarity, median (min-max)	23 (11-53)	17 (10-37)	p= 0.006
Polarity of first episode:			
Depressive episode onset (n)	19	12	
Manic episode onset (n)	14	8	n/s
Mixed episode onset (n)	1	1	
Number of depressive episodes, median (min-max)	1 (0-8)	4 (0-25)	p= 0.031

Number of hypomanic episodes, median (min-max)	0 (0-4)	0 (0-28)	n/s
Number of manic episodes, median (min-max)	1 (0*-1)	2 (1-25)	p= <0.001
Number of mixed episodes, median (min-max)	0 (0-2)	0 (0-4)	n/s
Number of psychotic episodes, median (min-max)	1 (0-2)	2 (0-25)	p= 0.038
Number of hospitalizations, median (min-max)	1 (0-4)	2 (0-4)	p= 0.040
Lifetime psychosis, n (%)	25 (73%)	14 (66%)	n/s
Years of treatment delay from first episode, median (min-max)	1.0 (0-18)	8.0 (0-31)	p= 0.012
Medications (n):			
Antipsychotics	28	12	n/s
Lithium	6	3	n/s
Antidepressants	11	5	n/s
Mood stabilizers	12	9	n/s
Unmedicated, n (%)	2 (6%)	7 (33%)	p= 0.008
Ongoing substance abuse/dependency (n)	4	2	n/s

[1]Data missing for 4 FM participants
*First episode mixed

Table 3: Neurocognitive functioning in first contact mania and healthy control participants.

	FM (n= 34) Mean (SD)	PM (n= 21) Mean (SD)	HC (n= 110) Mean (SD)	ANOVA F	P	η^2	Post hoc (Scheffè)
Learning and memory							
Logical memory (WMS-III):							
Learning (LM 1)	24.9 (7.9)	24.9 (4.5)	26.5 (6.5)	$F_{(2,162)} = 1.0$	0.381	.01	
Recall (LM 2)	20.9 (8.2)	21.4 (5.3)	23.8 (7.2)	$F_{(2,162)} = 2.5$	0.084	.03	
CVLT-II:							
Learning (list A total trials 1-5)	53.8 (13.7)	54.0 (10.6)	57.2 (9.2)	$F_{(2,162)} = 1.9$	0.158	.02	
Long delay free recall	11.3 (4.2)	12.5 (3.0)	13.2 (2.4)	$F_{(2,162)} = 5.2$	0.007*	.06	FM < HC
Rey-Osterrieth Complex Figure Test:[1]							
Delayed recall	20.8 (7.5)	19.1 (6.0)	22.8 (6.1)	$F_{(2,161)} = 3.6$	0.030	.04	
Psychomotor speed							
Grooved Pegboard:							
Average of both hands combined	74.7 (16.0)	77.4 (16.6)	64.0 (7.7)	$F_{(2,162)} = 20.2$	<0.001*	.20	FM,PM < HC
Digit symbol Coding (WAIS-III)	66.8 (14.8)	67.6 (14.3)	78.1 (14.6)	$F_{(2,162)} = 10.5$	<0.001*	.11	FM,PM < HC
Color-Word Interference Test (D-KEFS):							
Color naming	31.6 (7.3)	32.2 (9.2)	28.2 (4.8)	$F_{(2,162)} = 6.6$	0.002*	.08	FM,PM < HC

completion time							
Word reading completion time	22.1 (3.5)	23.1 (4.4)	21.5 (3.3)	$F_{(2,162)} = 1.8$	0.161	.02	
Attention / working memory							
Digit span (WAIS-III):							
Forward	5.9 (1.2)	6.0 (1.3)	6.2 (1.1)	$F_{(2,162)} = 1.1$	0.329	.01	
Backward	4.1 (1.1)	4.3 (1.2)	4.8 (1.2)	$F_{(2,162)} = 4.8$	0.009*	.06	FM < HC
Letter-Number sequencing [2]	9.6 (3.1)	9.4 (2.4)	11.2 (2.3)	$F_{(2,161)} = 8.1$	<0.001*	.09	FM,PM < HC
Bergen n-back, *d'* [3]	3.2 (1.1)	3.0 (1.2)	3.4 (0.8)	$F_{(2,144)} = 1.2$	0.311	.02	
Executive functioning							
Verbal Fluency Test (D-KEFS):							
Letter fluency total correct	41.3 (13.3)	42.3 (13.6)	43.0 (10.1)	$F_{(2,162)} = 0.3$	0.755	<.01	
Category fluency total correct	44.9 (11.0)	45.8 (11.7)	48.9 (8.5)	$F_{(2,162)} = 1.6$	0.208	.02	
Category switching total correct	14.0 (2.8)	14.5 (3.6)	14.9 (2.4)	$F_{(2,162)} = 1.6$	0.199	.02	
Color-Word Interference Test (D-KEFS):							
Inhibition completion time	59.9 (26.6)	61.1 (18.9)	49.4 (10.5)	$F_{(2,162)} = 8.2$	<.001*	.09	FM,PM < HC
Inhibition/switching completion time	60.9 (25.4)	65.1 (20.6)	55.6 (12.5)	$F_{(2,162)} = 3.5$	0.033	.04	

WCST:[4]							
Total errors	15.4 (7.2)	15.6 (6.2)	14.4 (6.4)	$F_{(2,110)} = 0.3$	0.713	<.01	
Perseverative responses	7.8 (3.5)	7.5 (3.3)	7.1 (3.7)	$F_{(2,110)} = 0.3$	0.703	<.01	
Categories	3.8 (1.2)	3.7 (1.3)	3.7 (1.2)	$F_{(2,110)} = 0.4$	0.962	<.01	
IQ:							
Vocabulary	60.3 (8.8)	61.2 (6.6)	60.6 (7.3)	$F_{(2,162)} = 0.1$	0.902	<.01	
Similarities	37.4 (5.1)	37.9 (4.1)	38.5 (5.2)	$F_{(2,162)} = 0.5$	0.555	<.01	
Block design	47.2 (15.9)	46.0 (12.2)	55.6 (10.2)	$F_{(2,162)} = 10.4$	<.001*	.11	FM,PM < HC
Matrix reasoning	27.8 (5.8)	25.7 (4.8)	28.2 (3.3)	$F_{(2,162)} = 3.2$	0.042	.04	
Full scale IQ	108.6 (14.7)	106.9 (9.6)	111.6 (11.4)	$F_{(2,162)} = 1.8$	0.159	.02	

* Significant after Bonferroni corrections

LM: Logical Memory; WMS-II: Wechsler Memory Scale; CVLT-II: California Verbal Learning Test; WAIS-III: Wechsler Adult Intelligence Test; D-KEFS: Delis-Kaplan Executive System; WCST: Wisconsin Card Sorting Test.

[1]RCFT scores missing for 1 HC
[2]L-N sequencing missing for 1 HC
[3]Bergen n-back scores missing for 7 FM, 4 PM and 7 HC
[4]WCST scores missing for 8 FM, 6 PM and 38 HC

Table 4: Clinical impairment in first contact mania and healthy control participants

	Cut-off score	FM	PM	HC	Group comparisons	
	(z < -1.5)	(n = 34), n (%)	(n= 21), n (%)	(n= 110), n (%)		
Learning and memory						
Logical memory (WMS-III)						
Learning (LM 1)	< 16.7	7 (20%)	1 (5%)	4 (4%)	$\chi^2_{(2, n=165)}$= 11.3, p= .004	FM < PM, HC
Recall (LM 2)	< 12.9	6 (18%)	3 (14%)	6 (5%)	$\chi^2_{(2, n= 165)}$= 5.4, p= .065	
CVLT-II:						
Learning (list A total trials 1-5)	< 43.3	9 (26%)	4 (19%)	6 (5%)	$\chi^2_{(2, n= 165)}$= 12.6, p= .002	FM,PM < HC
Long delay free recall	< 9.6	11 (32%)	2 (9%)	11 (10%)	$\chi^2_{(2, n= 165)}$= 10.9, p= .004	FM < PM,HC
Rey-Osterrieth Complex Figure Test:						
Delayed recall	< 13.6	7 (20%)	4 (19%)	11 (10%)	$\chi^2_{(2, n= 164)}$= 3.1, p= .211	

Psychomotor speed						
Grooved Pegboard:						
Average of both hands combined	< 52.4	12 (35%)	9 (43%)	9 (8%)	$\chi^2_{(2, n= 165)}$= 22.7, p <.001	FM, PM < HC
Digit symbol coding (WAIS-III)	< 56.2	7 (20%)	5 (24%)	7 (6%)	$\chi^2_{(2, n= 165)}$= 8.7, p= .013	FM, PM < HC
Color Word Interference Test (D-KEFS):						
Color naming completion time	< 21.0	6 (18%)	3 (14%)	8 (7%)	$\chi^2_{(2, n= 165)}$= 3.4, p= .179	
Word reading completion time	< 16.6	4 (12%)	4 (19%)	9 (8%)	$\chi^2_{(2, n= 165)}$= 2.3, p= .309	
Attention / working memory						
Digit span (WAIS-III)						
Forward	< 4.5	4 (12%)	2 (9%)	6 (5%)	$\chi^2_{(2, n= 165)}$= 1.7, p= .424	

Backward	< 3.0	2 (6%)	1 (5%)	1 (<1%)	$\chi^2_{(2, n= 165)}$= 3.3, p= .195	
Letter-Number sequencing	< 7.7	9 (26%)	3 (14%)	5 (4%)	$\chi^2_{(2, n= 164)}$= 13.7, p= .001	FM < PM, HC
Bergen n-back test:						
d'	< 2.2	3 (9%)	4 (19%)	9 (8%)	$\chi^2_{(2, n= 147)}$= 3.3, p= .193	
Executive functioning						
Verbal fluency test (D-KEFS):						
Letter fluency total correct	< 33.6	5 (15%)	3 (14%)	6 (5%)	$\chi^2_{(2, n=165)}$= 3.9, p= .142	
Category fluency total correct	< 35.2	8 (23%)	2 (9%)	8 (7%)	$\chi^2_{(2, n= 165)}$= 7.1, p= .029	FM< PM, HC
Category switching total correct	< 11.4	4 (12%)	3 (14%)	8 (7%)	$\chi^2_{(2, n=165)}$= 1.4, p= .492	
Color-Word interference (D-KEFS)						

Inhibition completion time	< 33.6	11 (32%)	5 (24%)	9 (8%)	$\chi^2_{(2, n=165)}$= 13.2, p= .001	FM, PM < HC
Inhibition/switching completion time	< 36.8	5 (15%)	2 (9%)	7 (6%)	$\chi^2_{(2,n= 165)}$= 2.4, p= .307	
WCST						
Total errors	< 4.8	4 (12%)	2 (9%)	5 (4%)	$\chi^2_{(2, n= 113)}$= 1.8, p= .406	
Pers. responses	< 1.5	3 (9%)	1 (5%)	6 (5%)	$\chi^2_{(2, n= 113)}$= 0.3, p= .841	
Categories	< 1.9	0 (0)	1 (5%)	3 (3%)	$\chi^2_{(2, n= 113)}$= 1.5, p= .480	
IQ (WASI)						
Vocabulary	< 49.6	6 (18%)	2 (9%)	8 (7%)	$\chi^2_{(2, n= 165)}$= 3.1, p= .203	
Similarities	< 30.7	3 (9%)	0 (0)	8 (7%)	$\chi^2_{(2, n= 165)}$= 1.8, p= .403	
Block design	< 40.3	8 (23%)	7 (33%)	10 (9%)	$\chi^2_{(2, n= 165)}$= 10.4, p= .006	FM, PM < HC
Matrix reasoning	< 23.2	6 (18%)	7 (33%)	11 (10%)	$\chi^2_{(2, n= 165)}$= 8.0, p= .018	PM < FM, HC

WMS-II: Wechsler Memory Scale; CVLT-II: California Verbal Learning Test; WAIS-III: Wechsler Adult Intelligence Test; D-KEFS: Delis-Kaplan Executive System; WCST: Wisconsin Card Sorting Test; WASI: Wechsler Abbreviated Scale of Intelligence.

Table 5: Association between neurocognition and clinical symptoms in the first contact mania group (FM and PM combined) (Spearman's rho).

	Age at onset	Treatment delay	Number of psychotic episodes	Number of manic episodes	Number of depressive episodes	PANSS positive	PANSS negative	IDS-C	YMRS	DDD[5]
Logical memory:										
Learning	-0.14	0.04	0.00	0.04	0.20	0.12	0.09	0.20	0.13	-0.06
Recall	-0.16	<0.01	-0.06	0.12	0.20	0.02	0.04	0.18	0.14	-0.18
CVLT-II[1]:										
Learning	-0.16	0.03	0.07	0.04	0.22	-0.01	-0.04	0.11	0.04	-0.23
Recall	-0.26	0.15	-0.06	0.20	0.33	-0.04	-0.14	0.13	0.09	-0.29
RCFT[2]:										
Recall	0.18	-0.16	-0.06	0.04	0.04	-0.09	-0.04	-0.23	-0.05	-0.09
Grooved pegboard:										
Avr. Both h.	0.07	0.04	0.17	-0.17	-0.17	-0.04	0.15	0.06	-0.10	0.39**
Digit symbol	-0.07	-0.12	-0.10	0.06	0.06	-0.07	-0.02	-0.06	-0.10	-0.25
Digit span:										
Forward	-0.09	0.08	-0.02	0.20	0.05	-0.05	-0.17	0.10	-0.01	-0.06
Backward	0.10	-0.21	0.03	0.04	0.12	-0.07	0.11	0.05	-0.18	0.01
Letter-number sequencing	-0.12	-0.16	-0.02	0.09	-0.02	-0.15	-0.03	0.02	-0.18	-0.14

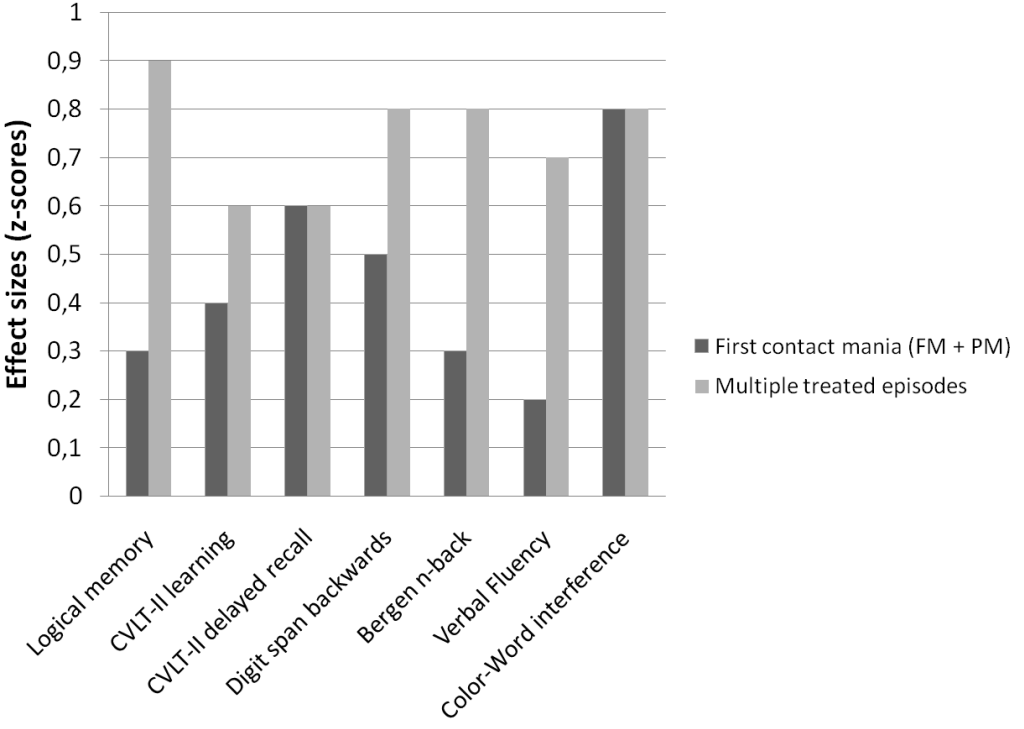
Bergen n-back test:										
d'	0.06	-0.16	0.03	0.13	0.10	-0.05	0.03	-0.02	-0.17	-0.08

Verbal fluency:										
Phonetic	-0.08	0.12	-0.23	-0.03	0.09	-0.16	0.06	0.19	-0.14	-0.05
Semantic	-0.23	-0.03	-0.18	-0.03	0.14	-0.07	0.09	0.12	-0.07	-0.01
Set shift	-0.16	0.08	-0.15	0.09	0.22	0.01	0.05	0.35	-0.05	-0.14
CW-Interference[3]:										
Color naming	0.01	0.04	0.04	0.01	0.00	0.13	0.06	0.30	0.10	-0.09
Word reading	-0.15	0.08	0.30	0.25	0.02	0.11	-0.05	0.09	0.15	0.07
Inhibition	0.15	0.02	0.11	0.09	-0.12	0.12	-0.01	0.13	0.18	0.06
Set shift	0.15	0.11	0.14	0.15	-0.05	0.17	-0.06	0.15	0.15	-0.07
WCST[4]:										
Total errors	0.23	-0.12	0.08	0.03	-0.15	0.11	-0.28	-0.29	0.24	0.02
Pers. resp.	0.23	-0.06	0.03	-0.02	-0.11	0.09	-0.21	-0.26	0.14	0.08
Categories	-0.16	0.08	0.01	0.04	0.17	-0.19	0.08	0.26	-0.19	-0.20
IQ:										
Vocabulary	0.09	0.16	-0.04	0.18	0.02	-0.11	0.09	0.16	-0.23	-0.01
Similarities	-0.14	0.21	-0.08	0.14	0.28	-0.09	0.19	0.22	-0.23	-0.26
Block design	0.16	-0.18	-0.14	0.00	-0.09	-0.04	0.00	-0.16	0.01	-0.20
Matrix reasoning	0.04	-0.19	-0.20	-0.13	-0.06	.013	-0.08	0.04	0.13	-0.13

[1] California Verbal Learning Test-II
[2] Rey Osterrieth Complex Figure Test
[3] Color-Word Interference Test
[4] Wisconsin Card Sorting Test
[5] Defined Daily Dose antipsychotic medication

** significant at 0.01 level

Figure 1: Patient-control performance in first contact mania (FM and PM groups combined) and multiple-treated episodes BD



III

Social functioning in first contact mania: clinical and neurocognitive correlates.

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Abstract

Purpose: To study the association between neurocognition and social functioning in patients having their first treatment contact for bipolar disorder.

Methods: A total of 55 first contact patients, 34 with a first manic episode (FM) and 21 with previously untreated manic episodes (PM), and 110 healthy control subjects matched for age, sex and education to the patient group, completed the Social Functioning Scale (SFS), a self-reported assessment of social functioning. The patients' level of functioning was rated by a clinician using the split Global Assessment of Functioning- Function scale (GAF-F), and they completed a broad neuropsychological test battery.

Results: Both patient groups had significantly lower self-rated social functioning compared to healthy controls, measured by the SFS. In addition, PM patients reported significantly lower functioning than FM patients. In multivariate analyses exploring the relationship to clinical symptoms and neurocognition, current depressive symptoms and processing speed had an independent influence on self-rated social functioning, while only current psychotic symptoms had an independent relationship to clinician-rated social functioning.

Conclusions: Social dysfunction was present in patients with BD already at first treatment contact episode, the main predictors of this being the severity of clinical symptoms. Patterns of association were different for self-rated compared to clinician-rated functioning.

Keywords: social functioning; bipolar disorder; neurocognition; manic episode.

Word count, abstract: 202

Introduction

Bipolar disorder (BD) is one of the largest causes of disability in developed countries and ranks amongst the leading contributors to global burden of disease worldwide [1]. BD is considered to have a more favourable prognosis than schizophrenia, but psychosocial dysfunction is not uncommon [2] and 30-60% of BD patients have detectable levels of social impairment in both occupational and social realms [3]. In a recent study (N=1656) of outpatients with BD, 64% had achieved clinical- but only 34% achieved functional recovery after 2 years [4], in line with previous studies demonstrating lack of functional recovery despite syndromal remission [5-7]. The areas most negatively affected appear to be social relationships and family life. Despite similar levels of education as the general population [8], BD patients are also reported to have lower social and occupational functioning [9], including lower annual income, and a higher risk of receiving disability pension or being unemployed [8,10]. The annual number of lost work days is also higher than for persons with major depressive disorder [11,12].

The factor most commonly associated with social dysfunction appears to be syndromal- or subsyndromal depressive symptoms [13-20]. Number of previous depressive episodes seems negatively related to impairments of social life, and number of previous manic episodes to impairments of work- and family life [21]. In direct comparisons, previous episodes of depression appears to be a stronger determinant of outcome than previous episodes of mania [3,22,23]. Findings regarding other clinical characteristics, such as age at onset, duration of illness, total number of episodes or the presence of psychotic symptoms, are less conclusive [9].

Cognitive dysfunction is an important predictor of social dysfunction in severe mental disorders, particularly in schizophrenia where it by many is considered the most significant contributor to functional loss [24]. Cognitive dysfunction is also found to be significantly

associated with psychosocial functioning in 6 of 8 studies of euthymic BD patients, and in 5 of 5 studies of symptomatic BD patients [25]. Deficits in various areas of neurocognition such as verbal memory [13,26-28] attention [28], executive functioning [13,26-28] and processing speed [17], have been linked to social dysfunction or to prediction of long-term functional outcome in BD. The longitudinal relationship is however unclear, since most studies are from chronic patient samples, and it is possible that both depression and cognitive dysfunction occur more frequently later in the course of BD. To better investigate mechanisms behind social dysfunction in BD, separating clinical factors from the confounding influence of failed treatments and social marginalization, we need studies following patients from their first treatment contact. Studies of social dysfunction in early phase BD are however very rare, and the pioneering studies comprise mainly hospitalized and/or psychotic patients and do not include measures of neurocognition [29,30]. The recent Systematic Treatment Optimization Program for Early Mania (STOP-EM) project found significantly social- and neurocognitive dysfunction in BD patients even at first treatment contact [16], and a six month follow-up of clinically stable patients (N=45) found that baseline verbal learning and memory was robustly associated with functional- but not clinical outcome in this group [31].

The current study is based on an extensively clinically, neurocognitively and functionally characterized cohort of patients coming to their first treatment for a manic episode (i.e. *first contact* mania patients). Thereby including both patients experiencing their first lifetime manic episode lifetime, in addition to patients with one or more previously untreated manic episodes.

Our main aims are to provide a comprehensive characterization of social functioning using both clinician-rated and self-report measures and to examine the relationship between current social functioning (self-reported and clinician-rated), and neurocognition, age at onset, premorbid adjustment and current clinical symptoms.

Materials and methods

Participants

Participants were recruited consecutively to the Thematically Organized Psychosis (TOP) Study from psychiatric inpatient and outpatient units at hospitals in the Oslo area. Patients were eligible for this particular study if they met the diagnostic criteria for DSM-IV [32] BD type I and received their first adequate treatment for a manic episode (i.e. defined as *first contact* mania). Patients who had experienced previously untreated manic episodes, or had experienced and/or received treatment for a major depressive episode could also be included in the study. Some acute patients were unable to give informed consent at first contact due to severe and disruptive symptoms, but were given the opportunity to enter up to one year after the start of first treatment. A total of 55 patients met these inclusion criteria. In the analysis, this patient group was divided into two groups: the First Manic episode group (FM), had experienced only one manic episode, and the Previous Manic episodes group (PM), had experienced previous untreated manic episodes. Healthy control (HC) participants were randomly selected from national statistical records from the same catchment area as the patients and contacted by letter inviting them to participate. HC participants were excluded if they or any close relative had a lifetime history of a psychiatric disorder (schizophrenia, BD and major depression), or if they had substance abuse or dependency in the last six months. For the purpose of this study, consecutive HC participants were matched in a ratio of 2:1 to each patient based on age, gender and education. Exclusion criteria for all groups were a history of head injury requiring hospitalization, presence of a neurological disorder, an unstable or uncontrolled medical condition that interferes with brain function, IQ below 70 and age outside the range of 17-60 years. The participants also had to have Norwegian as their first language or have received their compulsory schooling in Norway, in addition to a score of 15 or above on the forced recognition trial in the California Verbal Learning Test (CVLT-II) [33] to ensure adequate test effort. The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. All patients received a complete description of the study before giving written informed consent.

Clinical assessment

Trained psychiatrists and clinical psychologists carried out clinical assessment. Diagnosis, age at onset, number of previous mood episodes and information about lifetime presence of psychotic symptoms were based on the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) [34] and available medical records. Inter-rater reliability for diagnosis had an overall kappa-score of 0.77 (95% CI [0.60, 0.94]) [35]. The level of current symptomatology was assessed by the following scales: Current depressive symptoms were rated using the Inventory of Depressive Symptoms-Clinician rated (IDS-C) [36], current manic symptoms by the Young Mania Rating Scale (YMRS) [37], and current positive and negative symptoms by the Positive And Negative Syndrome Scale (PANSS) [38].

Assessment of social functioning

The Social Functioning Scale (SFS) [39] is a self-administered questionnaire consisting of 76 items arranged into seven subscales. Each subscale is standardized to a scaled score (SS) with a mean of 100 and standard deviation of 15, based on a sample of 334 outpatients with schizophrenia [39]. The SFS total score is the mean of the seven subscale SSs. High scores indicate a better performance than low scores. The seven subscales are: (1) Withdrawal (time spent alone, initiation of conversation, social avoidance); (2) Interpersonal behavior (number of friends, having a romantic partner, quality of communication); (3) Pro-social activities (engagement in common social activities, e.g. going to the cinema); (4) Recreation (engagement in common hobbies and interests); (5) Independence-competence (the ability to perform skills necessary for independent living, like shopping for groceries, doing laundry etc.); (6) Independence-performance (the actual performance of those same skills); (7) Employment (engagement in productive employment or a structured program of daily activity). The Norwegian version of the SFS is validated for use in both patients with schizophrenia and those with BD [40]. The scale was administered to all participants as part of the neuropsychological examination, and participants were given instruction on how to

complete the questionnaire by a trained psychologist, and were allowed to ask questions if they were uncertain of the meaning of any specific items. In addition to the SFS, the Global Assessment of Function (GAF) split version (GAF-Function and GAF-Symptom) [41] was used to measure clinician-rated social functioning. The scale is divided into ten equal intervals ranging from 1 to 100, where a score of 100 represents superior functioning. For the purpose of this study, only the function scale (GAF-F) was used as a measure of global social functioning. We used the Premorbid Adjustment Scale (PAS) to measure premorbid social functioning [42]. The PAS is designed to evaluate the level of functioning in four major areas during different periods of the subject's life, based on self-report: (1) social accessibility - isolation, (2) peer relationships, (3) ability to function outside the nuclear family and (4) capacity to form intimate socio-sexual ties. Items evaluating age-appropriate functioning in these areas are repeated for each period of the subject's life (Childhood < 11 years; Early Adolescence, 12-15 years; Late Adolescence, 16-18 years; and Adulthood > 19 years). Scores range from 0-6 where zero represents the best possible functioning. For the analyses, PAS scores were divided into two domains, Academic and Social, and for each domain, we discriminated between the initial level of functioning (childhood scores) and the change in level of functioning (difference between last premorbid score and initial score) [43].

Neurocognition

Psychologists trained in standardized neuropsychological testing carried out the neuropsychological assessment. A three-hour test battery including measures previously found to be sensitive to dysfunction in severe mental disorders [44,45] was administered in a fixed order with two breaks in between.

Verbal memory was tested with the Logical Memory test (LM-I) from the Wechsler Memory Scale-III (WMS-III) [46] and the Total List A 1-5 score from the California Verbal Learning Test-II (CVLT-II) [33]. *Processing speed* was assessed with the Digit Symbol test from the WAIS-III [47]. *Working memory* was assessed with Digit Span (forward and backward task) from the WAIS-III [47], and with d-prime (*d'*) from the Bergen *n*-back task [48]. *Verbal fluency* was measured with the Letter Fluency and Category fluency from the Verbal Fluency Test in

the D-KEFS battery [49]. *Interference control* was measured by the Inhibition and the Switching subtest from the Color-Word Interference Test in the D-KEFS battery [49]. Raw scores were reported for all tests. Analysis from our previous work [50] has shown significant differences between the two BD groups and the HC group on three of the ten chosen measures: Digit symbol, Digit span backward and the Color-Word Inhibition subtest, with the HC group performing better in all three. The clinical group also showed clinically significant cognitive impairment on all ten neuropsychological measures, defined as neurocognitive scores 1.5 SD below the average of the healthy control group. On average 17% of the two BD patient groups combined had clinically significant cognitive impairment.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS for Windows, version 16.0, SPSS Inc., Chicago, IL, USA) was used for all statistical analysis. Univariate analysis of variance (ANOVA) with Scheffès post hoc tests or Chi-square tests were used to compare FM, PM groups, and independent samples t-tests or Chi-square tests to compare the FM and PM groups. Due to small sample sizes and limited group differences the FM and PM groups were combined for the last sets of analyses. Non-parametric correlations (Spearman's rho) were used to assess the relationship between self-rated (SFS) and clinician-rated (GAF-F) social functioning with clinical and neurocognitive variables. Multiple regression analysis was carried out to explore the independent contribution of neurocognition and current symptomatology to self-rated (SFS) and clinician-rated (GAF-F) psychosocial function. We here included clinical and neurocognitive variables with an $\rho \geq .20$ to at least one of the functional measures in bivariate correlations. Clinical and premorbid variables were entered in block 1 and neurocognitive measures in block 2. The effect of insight on the relationship between SFS Total score and GAF-F was assessed using partial correlations and the PANSS G12 subscore as a measure of insight.

Results

Clinical and functional characteristics

Demographic characteristics of the FM, PM and HC groups are presented in table 1 (TABLE 1 IN HERE). Measures of symptom severity and clinician-rated social functioning for the clinical groups (FM and PM) are presented in table 2 (TABLE 2 IN HERE). Both clinical groups showed good premorbid functioning (low PAS scores) with little change during the premorbid period, and with no significant differences between the groups. The median (min-max) age at onset for the FM group was 23 (11-53) years and 17 (10-37) years for the PM group ($p < 0.05$). At the time of assessment, both clinical groups had a moderate symptom load and functional impairment, as indicated by the GAF-S and the GAF-F levels. The groups also had low levels of current psychotic (PANSS-P), negative (PANSS-N) or manic (YMRS) symptoms. The median IDS-C score indicated that the patients were mildly depressed. The PM group had, as expected, significantly more depressive, manic and psychotic episodes as well as more hospitalizations and a longer treatment delay before first treatment compared to the FM group. The majority of participants were single, with no significant group differences regarding marital status. The groups however differed significantly on work ability; while the majority of FM participants were working or studying, the majority of the PM participants were on medical leave.

Self-rated social functioning in BD and HC participants

There were significant group differences between healthy controls and the two clinical groups for all SFS sub scales and the total score (Table 3) (TABLE 3 IN HERE). In addition, the FM and PM groups differed significantly from each other for the Independence-Competence, Prosocial Activities and Employment sub-scales, as well as the SFS Total score. The PM group rated themselves as less competent in performing independent living skills, participated less in social activities, were less likely to be engaged in full-time employment and had a lower overall SFS score compared to the FM group. Effect sizes were small to medium, with the

largest effect sizes for Independence-competence, Employment and SFS Total score. There was a small, but statistically significant, association between the two measures of social functioning, the SFS Total score and GAF-F (ρ=0.29, p=0.05). Controlling for insight had little effect on the relationship between the SFS Total score and the GAF-F.

The relationship between social functioning and clinical and neurocognitive measures.

A total of seven clinical variables correlated significantly ($\rho \geq .20$) with at least one measure of social functioning (four for the SFS and three for the GAF-F) (Table 4) (TABLE 4 IN HERE). For the SFS, these variables included cannabis use, current depression and number of depressive episodes. There was also a significant correlation between age at onset and SFS, indicating that better functioning was associated with later onset of BD. There were no significant associations between any measures of premorbid social adjustment and current social functioning measured by the SFS. In addition, the level of current PANSS positive-, depressive- and manic symptoms were all statistically significantly associated with the GAF-F. There were no significant correlations between any measures of premorbid social functioning and the GAF-F.

Neurocognitive variables (raw scores' mean (SDs)) are presented in table 5 (TABLE 5 IN HERE). There were no statistically significant correlations between neither self-rated social functioning (SFS Total score) nor clinician-rated social functioning (GAF-F) and neuropsychological test performance. Three of the neurocognitive tests representing the domains of processing speed and working memory correlated $\rho \geq .20$ with SFS Total score or GAF-F, and were chosen for further exploration in multiple regression analysis. An inspection of the partial correlation suggested that controlling for group membership (FM, PM) would not affect the relationship between clinical variables and self- or clinician-rated social functioning. The same result was also found for the neurocognitive variables.

Clinical and cognitive predictors of baseline social functioning

(TABLE 6 IN HERE). For the SFS, current level of depression (IDS-C) was the only clinical characteristic that remained in the final model (Table 6). Neither premorbid social functional level, current cannabis use, current psychotic/manic symptoms nor number of depressive episodes had any statistically significant influences after controlling for current levels of depression. Of the three selected neurocognitive variables, only Digit symbol test had a statistically significant influence in the multiple regression analyses, indicating that good processing speed was related to lower self-rated social functioning. Neither the Verbal fluency letter subtest nor the Digit span backward subtest contributed. Analysis of the same sets of variables with social functioning (GAF-F) showed that only the PANSS-Positive scale contributed significantly to the model. Adding group membership (FM vs PM) to the final step of the analysis did not change individual contributions, but only had a significant effect on self-rated social functioning but not on clinician-rated social functioning.

Discussion

The main finding of the study is that social dysfunction is present in patients with BD I already at their first treatment contact. Both the FM and PM groups scored significantly lower on all subscales of the SFS compared to healthy controls. In addition, PM patients rated themselves significantly lower than FM patients for the Independence-Competence, Prosocial activities and Employment subscales, had significantly lower SFS Total scores and also poorer occupational functioning. This confirms and expands findings from previous studies of various BD subgroups [3,4,16,51], with data of early signs of social dysfunction and of increasing dysfunction with increasing number of untreated episodes.

The main predictors of reduced functioning in the patient groups were clinical symptoms, in particular current depression that had the strongest independent contribution in

multivariate analyses. Neurocognitive functioning, with the possible exception of processing speed as measured by the Digit symbol test, did not appear to play an important role as a contributor to differences in social functioning, at least at this stage of the disorder. That the PM group tended to rate themselves as more impaired than the FM group patients with a first episode, may not necessary relate to the negative influence of manic episodes since the groups also differed concerning several other important clinical characteristics. The PM group had a longer treatment delay before first treatment, an earlier age at onset and more previous depressive and psychotic episodes. Both age at onset and number of depressive episodes have previously been found associated with reduced social functioning [52-54], with indication that the greatest decrease in function occurs relatively early in the course of illness [54].

Ongoing depressive symptoms were significantly associated with both lower self- and clinician-rated social functioning. The relationship between current depressive or subclinical depressive symptoms and social dysfunction in BD has also been consistently reported in previous studies [13-17,19,28]. Manic and psychotic symptoms were however mainly associated with lower clinician-rated social functioning. These findings are in line with previous studies of more chronic patients reporting increasing family friction already at the stage of hypomanic symptoms [55] and stepwise progression in disability with each increment of elevated mood [56]. In line with previous studies reporting an association between social dysfunction and substance use disorders [57,58] or excessive substance use [59], we found a significant association between life-time cannabis use and poorer self-rated social functioning in bivariate, but not in multivariate analyses. We also did not find any association between premorbid adjustment and social functioning, most probably because the patient group did not show any sign of premorbid dysfunction. The few previous studies on premorbid functioning in BD are conflicting, with findings both of reduced premorbid adjustment [60] and of normal adjustment [61]. Our findings support the notion that dysfunction in BD primarily develops in connection with clinical episodes and not earlier, as often seen in schizophrenia.

We found no significant correlations between neurocognition and self- or clinician-rated social functioning in bivariate analyses, in contrast to previous findings [13,17,26-28],

including a study of previously treated BD patients from our own study group [44]. Our current findings are however more in accordance the only previous study of first-episode BD [31], that found a lack of associations between baseline neurocognition and concurrent baseline psychosocial functioning in newly diagnosed patients with BD. Baseline cognitive functioning however predicted 6-month functional outcome. One possible explanation for the lack of association at this point of time is that the relatively high symptom levels during the first treatment phase may confound the relationship between cognition and baseline social functioning. Our finding that correcting for current levels of depression actually revealed a significant relationship between processing speed (Digit symbol test) and SFS total score not observable in the bivariate analysis may be a sign of this. The particular finding showed that both high current levels of depression and good processing speed had independent contributions to self-rated social dysfunction.

Our findings thus point to different predictors of self- and clinician rated social dysfunction. We have previously shown that the SFS measures slightly different aspects of social functioning than the GAF-F [40], as indicated by relatively low levels of association between the two measurements. The validity of self-report assessments in severe mental illness has been questioned [62]. Studies indicate that self-reports and reports by others agree more in the report of observable aspects such as functioning, than of psychological aspects where others actually tends to underestimate the severity [63]. We did not find that level of insight had any significant effect on the strength of the relationship between the SFS and the GAF-F, supporting the view that the lack of congruence is less a question of validity as of differences in underlying constructs. In line with this we conclude that since clinician-rated functioning relies more on observable aspects it also appears to be more influenced by severe psychopathology such as manic- or psychotic symptoms, while self-rated social functioning appears to be influenced by more subtle disturbances.

Patients with BD display comparative negative cognitive styles during depressive episodes to patients with unipolar depression. This includes low self-esteem, negative self-beliefs, self-blaming attributions and concerns about the need for achievement [64], which may cause depressed individuals to view themselves as more poorly functioning. Depressive periods are also characterized by decreased energy and social withdrawal. The basis for an association between good processing speed and lower self-rated social functioning can thus be

mediated by higher expectations and/or better awareness of own social functioning in persons with good cognitive functioning.

This study has several strengths and limitations. Strengths: This is one of the very first studies to examine the relationship between social functioning, clinical characteristics and neurocognition in a first contact BD cohort. We used reliable and valid self-report instruments that capture varied aspects of current and premorbid social functioning to measure social functioning in BD in addition to standard clinician-rated functional measures. Limitations: Patients were not euthymic as 60% of patients were at least mildly depressed, but since it was our goal to include patients as early in their disease course as possible i.e. in a period with relatively high levels of symptomatology, settling for complete euthymia would have delayed assessments considerably. The number of previous mood episodes was determined retrospectively and as always with retrospective reporting, there is a potential for bias although efforts were made to confirm through medical records.

Conclusion:

Impairment of social functioning is present in patients with BD as early as after their first treated manic episode. Patients with previous mood episodes and a longer treatment delay reported more social impairment and were less likely to be engaged in full-time employment or education than the rest of this first-contact group. Clinical symptoms were the most significant predictors of both self-rated and clinician-rated social functioning, with current depression associated with self-rated function and psychotic symptoms with clinician-rated function. Processing speed had a significant influence on social functioning, while other neurocognitive measures did not appear to play a significant role in social functioning at this point of time.

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Table 1: Demographic characteristics of the First manic episode (FM), Previous manic episodes (PM) and Healthy control (HC) groups

	First manic episode (FM) N= 34	Previous manic episodes (PM) N= 21	Healthy controls N= 110	Group comparisons
Age, mean (SD)	31.2 (9.6)	30.5 (10.6)	31.1 (9.8)	$F_{(2,162)} = 0.4$, p= 0.961
Sex, m/f (% males)	15/19 (44%)	8/13 (38%)	49/61 (45%)	$\chi^2_{(2, n= 165)} = 0.3$, p= 0.860
Years of education, mean (SD)	13.1 (2.2)	12.9 (2.3)	13.4 (1.9)	$F_{(2,162)} = 0.5$, p= 0.592
Premorbid (NART) IQ, mean (SD)*	110.9 (6.6)	109.5 (5.1)	111.6 (4.9)	$F_{(2,160)} = 1.3$, p= 0.259

NART: National Adult Reading Test

* FM: 1 missing; PM: 1 missing

Table 2: Clinical characteristics of the First manic episode (FM) and Previous manic episodes (PM) groups

	First manic episode (FM) N= 34	Previous manic episodes (PM) N= 21	Group comparisons
GAF-Symptom, mean (SD)	54.5 (15.3)	50.1(11.0)	n/s
GAF-Function, mean (SD)	47.7 (11.2)	48.9 (11.2)	n/s
PANSS Positive scale, mean score (SD) [Range]	11.6 (5.5) [7-27]	11.5 (3.8) [7-21]	n/s
PANSS Negative scale, mean score (SD) [Range]	9.6 (3.0) [7-20]	9.7 (3.8) [7-15]	n/s
Inventory of Depressive Symptoms – Clinician rated [1]			
Median score (min-max)	14 (0-39)	13 (0-50)	n/s
Young Mania Rating Scale, median score (min-max)	2 (0-28)	5 (0-19)	n/s
Age at first affective episode, any polarity, median (min-max)	23 (11-53)	17 (10-37)	p= 0.006
Number of depressive episodes, median (min-max)	1 (0-8)	4 (0-25)	p= 0.031
Number of manic episodes, median (min-max)	1 (0*-1)	2 (1-25)	p= <0.001
Number of psychotic episodes, median (min-max)	1 (0-2)	2 (0-25)	p= 0.038
Number of hospitalizations, median (min-max)	1 (0-4)	2 (0-4)	p= 0.040

Lifetime psychosis, n (%)	25 (73)	14 (66)	n/s
Years of treatment delay from first episode, median (min-max)	1.0 (0-18)	8.0 (0-31)	p= 0.012
Premorbid Adjustment Scale (PAS):			
Social cluster level, mean (SD)	0.9 (1.2)	1.3 (1.3)	n/s
Social cluster change, mean (SD)	-0.2 (1.1)	0.0 (1.3)	n/s
Academic cluster level, mean (SD)	1.3 (1.0)	1.6 (1.3)	n/s
Academic cluster change, mean (SD)	0.5 (1.2)	0.9 (1.3)	n/s
Marital status:			n/s
Married, n (%)	10 (29)	3 (14)	
Living with partner, n (%)	3 (9)	5 (24)	
Single, n (%)	18 (53)	12 (57)	
Divorced, n (%)	2 (6)	1 (5)	
Other, n (%)	1 (3)	-	
Work ability:			p= .006
Full time working or studying, n (%)	18 (53)	2 (10)	

Disability compensation, n (%)	5 (15)	4 (19)	
Medical leave, n (%)	5 (15)	10 (48)	
Other, n (%)	6 (18)	5 (24)	
Cannabis use lifetime, n (%)[2]	19 (56)	11 (52)	n/s

[1]Data missing for 4 FM participants
[2]Data missing for 2 PM participants
*First episode mixed

Table 3

Group differences between the First manic episode (FM) group, Previous manic episodes (PM) group and Healthy control (HC) group on the Social Functioning Scale (SFS)

	FM (n= 34)	PM (n= 21)	HC (n= 110)	F	p	η^2	Post hoc
Withdrawal	107.0 (8.9)	105.0 (11.2)	119.5 (8.9)	38.2	<.001	0.3	PM, FM < HC
Interpersonal behavior	122.2 (17.7)	116.2 (17.0)	136.6 (12.9)	25.0	<.001	0.2	PM, FM < HC
Independence – performance	105.4 (10.1)	99.7 (12.2)	116.2 (10.4)	29.6	<.001	0.3	PM, FM < HC
Independence – competence	109.3 (13.5)	102.6 (10.8)	121.4 (4.0)	68.2	<.001	0.4	PM < FM < HC
Recreation	112.4 (16.1)	106.2 (15.4)	125.4 (13.0)	23.5	<.001	0.2	PM, FM < HC
Prosocial activities	114.9 (12.1)	104.9 (14.7)	122.5 (11.0)	22.1	<.001	0.2	PM < FM < HC
Employment	111.7 (10.2)	106.2 (10.5)	121.5 (3.2)	66.5	<.001	0.4	PM < FM < HC
SFS Total score	111.8 (8.7)	105.8 (9.9)	123.3 (5.6)	76.4	<.001	0.5	PM < FM < HC

Table 4 Bivariate correlations between clinical variables and self- (SFS) and clinician-rated (GAF-F) social functioning for the combined First Contact Mania groups

Clinical variables	SFS		GAF-F		Chosen for multiple regression (r > .20)
	ρ	p	*ρ*	p	
PAS - Social cluster level	-0.23	0.097	0.13	0.340	X
PAS - Social cluster change	-0.12	0.384	-0.14	0.321	
PAS - Academic cluster level	0.14	0.314	-0.05	0.720	
PAS - Academic cluster change	-0.16	0.249	-0.07	0.609	
Cannabis	-0.35**	0.010	-0.17	0.212	X
PANSS-Positive	-0.24	0.075	-0.53**	0.000	X
PANSS-Negative	-0.14	0.299	-0.11	0.417	
IDS-C	-0.37**	0.008	-0.39**	0.009	X
YMRS	0.02	0.894	-0.36**	0.007	X
Age at onset	0.31*	0.022	0.19	0.156	X
Number of depressive episodes	-0.35**	0.009	-0.25	0.066	X
Lifetime psychosis	0.01	0.934	-0.14	0.303	

SFS: Social Functioning Scale; GAF: Global Assessment of Functioning; PAS: Premorbid Adjustment Scale; PANSS: Positive and Negative Syndrome Scale; IDS-C: Inventory of Depressive Symptoms- Clinician rated; YMRS: Young Mania Rating Scale

Table 5

Bivariate correlations between neurocognition and self- (SFS) and clinician-rated (GAF-F) social functioning for the combined First Contact Mania groups

			SFS		GAF-F		Chosen for multiple regression (r>.20)
	Mean (SD) FM + PM (n=55)	% with clinically significant impairment (1.5 SD < HC)	*ρ*	p	*ρ*	p	
Logical memory (LM1)	24.9 (6.8)	15 %	-0.17	0.229	0.05	0.690	
CVLT-II Learning (list A total trials 1-5)	53.8 (12.5)	24 %	-0.08	0.567	0.15	0.270	
Digit symbol	67.1 (14.5)	22 %	-0.25	0.067	0.16	0.256	X
VF Letter fluency total correct	41.6 (13.3)	15 %	-0.25	0.060	0.08	0.570	X
VF Category fluency total correct	45.2 (11.2)	18 %	-0.18	0.194	0.00	0.986	
Bergen n-back *d'*	3.1 (1.1)	16 %	-0.15	0.329	0.08	0.601	
Digit span forward	5.9 (1.2)	11 %	-0.16	0.253	0.12	0.392	
Digit span backward	4.2 (1.1)	7 %	-0.13	0.341	0.20	0.151	X
CW Inhibition completion time	60.3 (23.9)	29 %	0.06	0.636	-0.13	0.340	
CW Inhibition/switching completion time	62.5 (23.6)	13 %	-0.04	0.788	-0.19	0.156	

SFS: Social Functioning Scale; GAF: Global Assessment of Functioning; LM1: Logical memory-1; CVLT-II: California Verbal Learning Test-II; VF: Verbal Fluency Test; CW: Color-Word Interference Test

Table 6

Multiple regression models for clinical and cognitive variables associated with social functioning in the combined First Contact Mania groups

				Final model		
SFS		ΔR^2_{adj}	R^2_{adj}	β	p	ANOVA
Block 1	IDS-C	0.08	0.08	-0.35	0.012	
Block 2	Digit symbol	0.06	0.14	-0.27	0.046	$F_{(2,48)}$= 5.0, p= .010
GAF-F		ΔR^2_{adj}	R^2_{adj}	β	p	ANOVA
Block 1	PANSS-Positive	0.34	0.34	-0.59	<0.001	$F_{(1,53)}$=28.7, p<.001
Block 2	--	--	--	--	--	

SFS: Social Functioning Scale; GAF: Global Assessment of Functioning: IDS-C: Inventory of Depressive Symptoms- clinician rated; PANSS: Positive And Negative Syndrome Scale